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The Second-Generation Device of the Agency of Medical Innovations Used for Transanal Doppler-Guided Hemorrhoid Artery Ligation.

From the article on page 34

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Welcome to the Moldovan Medical Journal!

The journal was founded in 1958 on the initiative of Nicolae Testemitsanu, an outstanding expert in orthopedic surgery, social medicine and public health. From its debut the journal has striven to support the interests of Moldovan medicine concerning the new concepts of its development.

Since 2017 the owner of the journal has become the Scientific Medical Association of the Republic of Moldova and the journal continues to function as the scientific double-blind peer reviewed periodical edition issued 6 times per year designed for specialists in the areas of medicine, dentistry, pharmacy, social medicine and public health.

The Editorial Board warmly welcomes both the readers of and the authors for the journal, all those who are enthusiastic in searching new and more effective ways of solving numerous medicine problems. We hope that those who want to make their contribution to the science of medicine will find our journal helpful and encouraging.

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RESEARCH STUDIES

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The assessment of different tuberculosis-related features in Moldova regions

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Abstract

Background: Tuberculosis represents a social-related disease and for identifying the priority interventions for reducing its impact must be identified the main disparity features of patients.

Material and methods: Global Competitiveness Report and Report of the National Centre for Health Management were used. The clinical study was retrospective, randomized, selective, and included 263 new pulmonary TB cases registered in three different Moldovan regions: Chisinau (center), Balti (north) and Cahul (south).

Results: Attributable risk identified that in Chisinau compared to Balti predominated patients in economical vulnerable state, without health insurance, GeneXpert MTB/ Rifampicin sensible and those who successfuly finished the treatment. In Balti compared to Chisinau predominated chronic alcohol abusers, co-morbid patients, severe pulmonary tuberculosis, direct addressing to the hospital, patients infected with GeneXpert MTB/Rifampicin resistant strains of Mycobacteria. The major differences between Chisinau and Cahul groups, with predominance in Chisinau were homeless, co-morbid patients and those who successfully finished the treatment course. In Cahul predominated patients with rural residence, direct addressed to the regional hospital and severe forms of tuberculosis. Comparing the Balti and Cahul groups was established the predominance in Cahul of patients with rural residence, in economically vulnerable state and patient's detection by general practitioner. In Balti predominated co-morbid patients, alcohol abusers, patients with severe forms of tuberculosis.

Conclusions: Reduction of health care inequality will be achieved through social assistance of vulnerable groups and improvement of the general public life.

Key words: tuberculosis, risk factors, inequalities.

Introduction

Tuberculosis represents a social disease. "It reflects the problems that transcend the conventional medical approach…It is the consequence of gross defects in social organization and errors in individual behavior" [3]. Despite progress in tuberculosis control epidemic indices are concentrated in social vulnerable and marginalized populations that often have limited access to health care and are difficult to be reached by screening methods [1]. According to the WHO list of high burden countries in the post-2015 era the Republic of Moldova (MD) was included in 21 countries with the highest estimated number of incident multidrug-resistant (MDR-TB) cases [10]. The World Health Organization regional strategy to Stop Tuberculosis established that without focusing on the social determinants, high TB burden countries are unable to achieve success in the elimination of the disease [8]. There were identified a large number of upstream and downstream social determinants that contribute to the disease control. The document highlighted upstream determinants that extend the disease epidemics: rapid urbanization and migration, increasing socioeconomic disparities, social and financial insecurities. On the other hand downstream social determinants that permit to control the disease were high quality health services delivered for vulnerable populations [5, 9]. The well defined TB control programmers are those that emphasize the disease outcome in vulnerable populations and incorporate the health equity in planning and implementation of the control activities [7]. The study was designed with the aim to assess tuberculosis-related features in the frame of country's disparity measures. The objectives were: 1. Comparative assessment of the national and regional socioeconomic, demographic and epidemiological data. 2. Evaluation of the risk factors, laboratory and radiological characteristics of patients from three selected different Moldovan regions (Chisinau, Balti and Cahul); 3. Establishment of the main tuberculosis-related features that differentiate the selected Moldovan regions.

Material and methods

For the evaluation of the national statistical data were used the reports of the Moldovan National Centre for Health Management and Global Competitiveness Report 2016 [11]. The clinical study was performed as a retrospective, randomized, selective, descriptive research targeting risk factors, microbiological and radiological peculiarities, as well as treatment outcome of 263 new pulmonary TB cases from three different Moldovan regions: Chisinau (center), Balti (north) and Cahul (south). Included criteria were: patients older than 18 years, new cases with pulmonary TB diagnosed through microbiological methods (including molecular-genetic methods), signed informed consent and patients registered in the period 01.01.2015-31.12.2015. The first Chisinau group included 185 patients diagnosed and therapeutically managed in the frame of medical specialized

organizations of Chisinau city (Chisinau group), the second group included 43 patients diagnosed and managed in the Clinical Municipal Hospital (dispensary of Phtysiopneumology) of Balti city (Balti group) and the third included 35 patients diagnosed and managed in the Cahul Regional Hospital (Cahul group). There were used social, epidemiological collection methods, statistical analysis, graphic representation and analytical assessment through Microsoft Excel XP soft. Accumulated material was tabled in simple and complex groups.

Results

According to the Global Competitiveness Report of 2016 the Republic of Moldova (MD) occupied the 100-th place from 138 assessed countries worldwide by the determinants of long-term growth and scored 3,86 points (from 1 to 7). It declined 16 positions from the previous assessment in 2015. The low ranking was the result of the bad situation in the public finance, banking default and negative change in the macroeconomic environment due to the recession in the eastern neigborhood countries. Moldova was assessed as a country at the first stage of the economic development among the 35 poorest countries in the world. According to the basic requirements in health care and primary education MD ranks on the 95th place assessed with 5.39 points (from 1 to 7). The low level in health care was due to uncertain national health policies and declining security in the most of all health-related sectors. According to the tuberculosis incidence the Republic of Moldova was on the 104th place and the business impact of tuberculosis – on the 88th place from the 138 evaluated countries. Assessing the above data it was estimated that MD remains a high risk zone showing an inadequate concern regarding social determinants of poverty-related diseases that represent the main barrier to achieve the health related Sustainable Millenium Development Goals. Despite increasing by 5 times the national public budget, the funding of healthcare sector was low: 1.192 million lei in 2005, 3.846 million lei in 2010 and 5.890 million lei in 2015. Reported to the gross domestic product it demonstrated the low level of the health care financing: 3,9% in 2005, 6,1% in 2010 and 5,7% in 2015 [11]. Accumulated evidence suggested that low health care funding contributed to the low screening of high risk and hard-to-reach groups (homeless, migrants, individuals living with HIV, drug users, poor persons), deficiency in performing an effective anti-tuberculosis treatment and lack of interventions to resolve social and economic problems of the patients [1].

The actual study was designed to incorporate health-related issues of TB morbidity into demographic measures. Statistical yearbook of the Republic of Moldova established a decreasing tendency of the most important social and demographic indices in the period 2013-2015 [1]. The stable Moldovan population decreased by 4.278 people from 3.559.497 in 2013 to 3.555.159 citizens in 2015. In 65 Moldovan towns, considered as the major infectious clusters were residing 1.492.165 Moldovan citizens (40,67% from the total population) in 2013, 1.502.996 (42,24% from the total population) in 2014 and 1.507.265 citizens (42,39% from the total population) in 2015. The urban population increased between 2013 and 2015 by 10.831 people, on the other hand the rural population decreased by 19.428 people at the same period of time. As a comparison the population of Chisinau city increased by 9.600 people, the population of Baltsi by 491 citizens and the population of Cahul decreased by 307 people at the same period of time. One of the most eloquent indices associated with the decreasing of the population was the emigration trend. The published data established the diminishing tendency of the emigration from the MD abroad. In 2010 emigrated 4.714 Moldovan citizens and in 2014 emigrated 2.374 persons. The most of the migrants were leaving the country for the Russian Federation: 3.110 persons in 2010 and 788 persons in 2014 and for Ukraine 2.663 persons in 2010 and 602 persons in 2014. The general mortality increased by 1.846 deaths in the MD and by 448 deaths in Chisinau. On the other hand during the same assessed period of time it was established the decreasing of mortality in Balti by 5 deaths and by 1.301 deaths in Cahul (tab. 1).

The main social-economical indices characterizing the incomes and living standard of the Moldovan population established the increasing twice of the average nominal monthly earning of employees from 2.971 lei in 2009 to 4.089 lei in 2014, the average size of monthly pension from 810 in 2009 to 1.087 in 2014, the subsistence level 1.373 lei in

Table 1

Comparative demographic indices of three selected Moldovan areas

Index	2013		2014		2015	
	abs.	%	abs.	%	abs.	%
Population of MD	3.559.437	-	3.557.634	-	3.555.200	-
Urban population	1.492.165	40,67	1.502.996	42,24	1.507.265	42,39
Population of Chisinau	800.601	22,49	804.476	22,61	809.600	22,77
Population of Balti	149.709	4,2	149.784	4,2	150.200	4,2
Population of Cahul	124.907	3,51	124.700	3,50	124.600	3,5
Mortality in MD	38.060	1,06	39.490	1,11	39.906	1,12
Mortality in Chisinau	5.996	15,75	6.772	17,15	6.444	16,15
Mortality in Balti	1 366	2,28	1 338	1,97	1 361	2,11
Mortality in Cahul	2561	6,72	3071	4,53	1260	1,95

Note: reference of the National Bureau of Statistics of the Republic of Moldova. Demographic situation in the Republic of Moldova.

Table 2

Comparative epidemiological indices of tuberculosis in three selected Moldovan localities

Index	2013		2014		2015	
	abs.	100.000 population	abs.	100.000 population	abs.	100.000 population
Total incidence in MD	3.656	102,7	3.305	92,9	2.870	80,7
Total incidence in Chisinau	755	94,1	659	81,7	579	71,7
Total incidence in Balti	192	128, 2	141	94.0	156	104.0
Total incidence in Cahul	97	77,7	119	95,5	81	65,0
Prevalence in MD	3.904	109,7	3.450	97,0	3.073	86,4
Prevalence in Chisinau	1008	125,6	878	108,8	808	100,1
Prevalence in Balti	203	135,6	162	108,0	161	107,3
Prevalence in Cahul	125	100,1	120	96,3	99	79,4
Mortality in MD	657	16,1	373	10,5	314	8,8
Mortality in Chisinau	87	10,8	81	10,0	56	6,9
Mortality in Balti	14	9,3	28	18,7	24	16
Mortality in Cahul	6	4,8	14	11,2	9	7,2

2010 and 1.627 lei in 2014. The total expenditure for public health increased in 2015 compared with 2014 from 1.036 to 1.519 million lei.

The Moldovan health care system is based on the universal access to major services through mandatory health insurance mechanism [1]. Compulsory health insurance policy costs on average 300 Euros per year. The financing of most health organizations is performed by the National Health Insurance Company, but the uninsured part of the population ranges from 20 to 25%, and depends on the demographic residence (30% of the rural population are uninsured), on the ethnicity (minorities are more frequently uninsured), and other social disadvantaged conditions [1]. Despite the free of charge TB diagnosis and treatment, the lack of insurance in an insurance-based health care system determines a low medical coverage of high risk groups, deficient active screening and poor disease control. It is important to underline that all specialized health services, including detection, diagnosis, anti-tuberculosis treatment and hospitalization (during the intensive phase) are free of charge regardless of the health insurance status of the patient. Medical staff specialised in pneumophtysiology and involved in the health care of TB patients included 219 in 2013 and 216 in 2014 pneumophtysiologists, that corresponds to 0,6 specialists/100.000 population. On the opposite health care sector, considered the most important chain involved in the detection of symptomatic TB patients is continually growing with a total number of 1792 family doctors legally registered in 2014, corresponding to 6,7 general practitioners/100.000 population [2].

In the global epidemiological context the major indices describing the spread of TB disease in the general population are: the global incidence (number of new cases and relapses reported at 100.000 population), prevalence and mortality. According to the report of the Moldovan National Centre for the Health Managemen during the period 2013-2015 it was registered an important decline of all TB indices. The global incidence in MD decreased between 2013 and 2015 by 22/100.000, in Chisinau by 22,4/100.000, in Balti by 24,2/100.000 and in Cahul by 12,7/100.000. A similar vector was established regarding the prevalence (the total number of TB patients) which decreased between 2013 and 2015 in MD by 23,3/100.000, in Chisinau by 25,5/100.000, in Balti by 28,3/100.000, in Cahul by 20,7/100.000 population [1]. Multiple causes were involved in this rapid decline: low rate of high risk groups investigated by active screening (annual chest radiological examination), high rate of migrants inaccessible to screening procedures, low level of the health care seeking behavior of the population, high rate of citizens with the lack of the insurance policy and high rate of the rural population with low accessibility to health care services. Mortality due to the progression of TB was very high, despite the continuous decreasing tendency. During the period 2013-2015 mortality decreased twice from 16,1 to 8,8/100.000 population in MD and from 10,8 to 6,9/100.000 population in Chisinau. In the other two regions the mortality increased: twice in Balti from 9,3 to 16/100.000 population and in Cahul from 4,8 to 7,2/100.000 population [2].

Distributing patients according to the sex it was established the predominance of men 138 (74,6%) in comparison with women 47 (25,4%), with a male/female ratio=2,93/1 in the Chisinau group, 31 (72,09%) men *vs.* 12 (27,90%) women, with male/female ratio=2,58/1 in the Balti group and 29 (82,95%) men *vs.* 6 (17,14%) women, with male/female ratio=4,83/1 in the Cahul group. Distribution of patients in age groups according to the WHO recommendations identified the same distribution of patients in all selected groups. The biggest one was 35-44 years age group: 52 (28,1%) patients in the Chisinau group, 14 (32,56%) patients in the Balti group and 12 (34,28%) patients in the Cahul group. While redistributing patients in two age groups (18-44 years old and >45 years) it was established the predominance of young patients (18-44 years) in all groups: 112 (60,5%) cases in the Chisinau group, 26 (60,46%) cases in the Balti group and 20 (57,14%) patients in the Cahul group.

Distributing patients according to the demographic fea-

tures it was established that patients from urban areas were statistically more frequent in Balti comparing with the Chisinau group (p<0,05) and Cahul groups (p<0,001). The patients from villages were more numerous in the Cahul than in the Chisinau and Balti groups (p<0,001). Extreme poverty at homeless patients was identified in the Chisinau group and no such cases were identified in the Cahul group. Summarizing the results of the biological characteristics of patients it was demonstrated that men from southern localities and young individuals from urban areas must be included in the lists of patients for active screening. In addition, extreme poverty as a risk factor identified mainly in the urban localities must be targeted by all social organizations for the improvement of the disease control (tab. 3).

Table 3

Repartition according to the sex, age groups and demographics

Biological indices	Sex	Chisinau	Balti	Cahul
		N=185 (M%)	N=43 (M%)	N=35 (M%)
Sex	Men	138 (74,59)	31 (72,09)	29 (82,85)
	Women	47 (25,41)	12 (27,90)	6 (17,14)
Young age (reproductive groups)	15-24 years	24 (12,97)	3 (6,98)	0
	25–34 years	36 (19,46)	9 (20,93)	8 (22,86)
	35-44 years	52 (28,11)	14 (32,56)	12 (34,28)
>45 years old	45-54 years	42 (22,73)	5 (11,63)	7 (20,00)
	55-64 years	24 (12,97)	8 (18,61)	7 (20,00)
	>65 years	7 (3,78)	7 (16,28)	1 (2,86)
Demographics	Urban	139 (75,13)	38 (88,37	8 (22,86) □ ■
	Rural	46 (24,86)	5 (11,63)	27 (77,14) □ ■
Others	Homeless	27 (14,59)	2 (4,65))	0 □

Note: ○ – statistical difference between groups of patients from Chisinau and Balti; □ statistical difference between groups of patients from Chisinau and Cahul; ▪ statistical difference between groups of patients from Balti and Cahul.

Distribution of the patients according to the economic status established that employed persons, in this way contributing to the health budget by paying taxes and health insurance policy were identified in a small number in all assessed groups. The largest group of unemployed patients without personal financial support for life was identified in the Cahul group, that statistically predominated compared to the Balti group (p<0,01). Retired individuals statistically predominated in Balti compared with Cahul due to the highest rate of the old patients in the Balti group (p<0,05). Patients with conventional income due to the disability constituted the smallest part of all groups. Patients without health insurance comprised two thirds of the Chisinau and Cahul groups, and statistically predominated compared to the Balti group (p<0,001). The table 4 revealed exposed data. Considering exposed data, *mass media* must inform the general population that specialised health care, full access to all disease-related diagnostic tools and specific treatment for TB are free for all Moldovan patients regardless of their social, economical and insurance status.

Table 4

Economical status of patients with pulmonary tuberculosis

Economical state		Chisinau	Balti	Cahul
N=185 (M%)		N=43 (M%)	N=35 (M%)	
Economically stable	Employed	25 (13,51)	8 (18,61)	6 (17,14)
Economically vulnerable	Unemployed	124 (67,03)	23 (53,49)	25 (71,43) ▪
	Retired	15 (8,11)	8 (18,61)	1 (2,86) ▪
	Students	7 (3,78)	1 (2,33)	0
	Disease disability	14 (7,57)	3 (6,97)	3 (8,57)
Patients without health insurance		139 (75,13)	23 (53,49) ▪	26 (74,28) ▪

Note: ○ - statistical difference between groups of patients from Chisinau and Balti; □ statistical difference between groups of patients from Chisinau and Cahul; ▪ statistical difference between groups of patients from Balti and Cahul.

The distribution of risk groups identified that the largest group was represented by the patients in the economically vulnerable state (unemployed, retired and students), without health insurance and social protection. Economically vulnerable persons in the Chisinau group were 146 (78,92%) and in Cahul group - 29 (82,86%) patients, that statistically predominated compared to the Balti group (p<0,001). The unemployed patients were more numerous in the Chisinau and Cahul groups comparing with the Balti group (p<0,001). Younger patients aged less than 44 years old were similarly distributed in all groups. Patients living in extreme poverty and without a stable place of living were the sixth part of the Chisinau group, but no such individuals were identified in the Cahul group. Co-morbid patients were one half of the Balti group and one third of the Chisinau group, and statistically predominated compared with the Cahul group (p<0,001). The co-morbid patients HIV-infected represented the fifth part of the Balti group and not a single HIV infected case was identified in the Cahul group. In this context Balti represented a locality highly affected by TB-HIV co-infection and it was twice more exposed than Chisinau. Diagnosis of chronic alcoholism was established in each third patient from the Balti group and statistically predominated compared with the Chisinau and Cahul groups (p<0,001). Drug users and patients with mental disorders were in a small number in all groups. Despite the fact that the contact with an infected source is the most important factor influencing the risk of morbidity, the rate of patients from clusters was very low in all three localities, due to the poor quality of the cross-investigation. The highest rate of the patients from

the clusters was identified in Balti and it can be explained by their management in the frame of the pneumophtysiology dispensary. Former detained patients were in a similar proportion in all three groups (table 5).

Table 5

Distribution of patients according to the risks

Risk groups N=185 (M%)		Chisinau N=43 (M %)	Balti N=35 (M%)	Cahul
Social	Vulnerable state	146 (78,92)	25 (58,14) ○ ■	29 (82,86)
	Young persons	112 (60,5)	26 (60,46)	20 (57,14)
	Extreme poverty	29 (15,68)	3 (6,96)	0
Co-morbid groups	Comorbid cases	50 (27,03)	23 (53,49) ○	3 (8,57) □ ■
	HIV positive	11 (5,94)	6 (13,95)	0
	Chronic alcoholism	13 (7,03)	12 (27,91) ○	2 (5,71)
	IDU	3 (1,62)	1 (2,32)	0
	Psychic diseases	4 (2,16)	3 (6,98)	0
Epidemiological risk groups	TB contacts	15 (8,11)	8 (18,61)	5 (14,28)
High risk groups	Migrants	24 (12,97)	7 (16,28)	6 (17,14)
	Former detained	9 (4,86)	2 (4,65)	1 (2,85)

Note: ○ – statistical difference between groups of patients from Chisinau and Balti; □ statistical difference between groups of patients from Chisinau and Cahul; ▪ statistical difference between groups of patients from Balti and Cahul.

Studying case-management and medical staff involved in the patient's detection and clinical-radiological forms it was established that the most of the patients from Chisinau were detected by family doctors, that statistically predominated compared to the Balti (p<0,001) and Cahul groups. Patient's detection by direct addressing to the general practitioner or specialist for long-lasting broncho-pulmonary clinical signs is defined the passive way of detection. It was used to detect the most of the patients from all groups: 147 (79.46%) cases of the Chisinau group, 37 (86.05%) patients of the Balti group and 34 (86,055) of the Cahul group. Two-thirds of the symptomatic patients from the Balti group were detected by specialists due to the case-management performed in the frame of pneumophtysiology dispensary of the clinical municipal hospital. Active way performed by radiological screening of high risk groups was used in the detection of the minor part of the selected patients that demonstrated the low quality of the disease control in the risk or hard-to-reach groups.

While assessing the microbiological results it was identified that one half of the Chisinau and Balti groups, and two thirds of the Cahul group were microscopic positive for acid-fast-bacilli (AFB), demonstrating their epidemiological danger to the healthy population. The highest rate of culture positive at Lowenstein or BACTEC medium patients was identified in the Balti group, followed by the Cahul group. Multidrug-resistant strains of *Mycobacteria* were more frequently identified in patients from Balti and less frequently in Cahul. Resistance to rifampicin strains revealed by molecular-genetic examination GeneXpert MTB/Rif was statistically more frequently identified in the Balti group compared to the Chisinau group. Lung infiltrative opacities complicated with destruction and extended more than three lung segments statistically predominated in the Balti group compared to the Chisinau and Cahul groups. Acute disseminated tuberculosis as well as pulmonary tuberculosis with extrapulmonary localization was identified in a low proportion of assessed groups (tab. 6).

Table 6

Case-management and disease-related characteristics of Moldovan groups

	Management characteristics	Chisinau N=185 (M%)	Balti N=43 (M%)	Cahul N=35 (M%)
Detectional way	Detected by GP (passive way)	103 (55,67)	8 (18,61) ○	14 (40,00) ■
	Detected by GP (active way)	28 (15,13)	6 (13,95)	1 (2,86)
	Detected by SP (passive way)	34 (18,38)	14 (32,56)	8 (22,86)
	Others	10 (5,41)	15 (34,89) ○	12 (34,28) □
Laboratory features	Microscopic positive	101 (54,59)	25 (58,14)	27 (77,14)
	Culture positive	99 (53,51)	34 (79,07) ○	21 (60,00)
	Conventional sensible TB	135 (72,97)	28 (65,12)	24 (68,57)
	Culture DST MDR-TB	36 (19.46)	13 (30,23)	5 (14,29)
	DST mono/poli-resistant TB	14 (7,56)	2 (4,65)	2 (5,71)
	GeneXpert Rif sensible	147 (79,46)	25 (58,14) ○	24 (68,57)
	GeneXpert Rif resistant	38 (20,54)	18 (41,86) ○	11 (31,43)
	Extensive TB in 1 lung	80 (43,24)	23 (53,49)	21 (60,00)
	Extensive TB in 2 lungs	26 (14,05)	20 (46,51) ○	7 (20,00) ■ □
	Lung destruction	106 (57,29)	28 (65,16)	28 (80,00) □
	Disseminated TB	15 (8,11)	4 (9,32)	3 (8,57)
	PTB with extrapulmonary localization	2 (1,08)	0	1 (1,33)

Note: GP - general practitioner, SP-specialist in pneumophtysiology, DST – drug sensibility testing, Rif – rifampicine, PTB- pulmonary tuberculosis; ○ – statistical difference between groups of patients from Chisinau and Balti; □ statistical difference between groups of patients from Chisinau and Cahul; ▪ statistical difference between groups of patients from Balti and Cahul

Treatment outcome was assessed using the standardized indices. The highest success rate was established in the Chisinau group and statistically predominated compared to the Balti and Cahul groups. The highest rate of died patients was established in the Balti group. Failed and lost to follow-up patients represented the lowest proportion of the selected groups. Patients from the Balti and Cahul groups were still continuing the treatment more frequently. The highest rate of non-available treatment outcome data was established in the Balti group (tab. 7).

Table 7

Treatment outcomes

	Outcomes	Chisinau N=185 (M%)	Balti N=43 (M%)	Cahul N=35 (M%)
SO	Success	109 (79,46)	23 (53,48)○	20 (57,14) □
	Died	11 (5,95)	7 (16,28)	2 (5,71)
	Treatment failure	2 (1,08)	1 (2,33)	2 (5,71)
	Lost to follow-up	2 (1,08)	0	2 (5,71)
Others	Continuing IR	6 (3,24)	2 (4,65)	0
	Continuing DOTS-Plus	23 (12,43)	9 (20,93)	9 (25,57)
	Non-available results	32 (17,29)	24 (55,81)○	0 □ ■

Note: SO – Standardized outcome according to the WHO definitions; ○ – statistical difference between groups of patients from Chisinau and Balti; □ statistical difference between groups of patients from Chisinau and Cahul; ■ statistical difference between groups of patients from Balti and Cahul; continuing IR – continuing individualized regimen, Continuing DOTS-Plus – continuing treatment for MDR-TB according to the DOTS-Plus regimen.

An important research outcome was the attributable risk (AR) for identifying the main disparities between selected regions. In the table 8 were represented only risk factors and features which exposed statistical difference between the selected areas. It was established the hierarchy of the major differences between the Chisinau and Balti groups, with their predominance in the Balti group: chronic alcohol abuse or diagnosis of chronic alcoholism, extensive pulmonary tuberculosis, patient's co-morbid status, direct addressing to the hospital, infection with GeneXpert MTB/Rifampicin resistant strains of *Mycobacteria*. As to the Chisinau group there predominated patients in the economical vulnerable state, without health insurance, infected with GeneXpert MTB/Rifampicin sensible strains of *Mycobacteria* and those who successfuly finished the treatment.

The major differences between patients from the Chisinau and Cahul groups, with predominance in the Cahul group were: rural residence, direct addressing to the Cahul regional hospital and tuberculosis complicated with lung destruction. In the Chisinau group predominated homeless, co-morbid patients and those that successfully finished the treatment. The differences between patients from the Balti and Cahul groups, with predominance in the Cahul group were: rural residence, economical vulnerable state, unemployment and patient's detection by general practitioner. In the Balti group predominated co-morbid patients, alcohol abusers or diagnosed with chronic alcoholism, patients with severe extensive tuberculosis complicated with lung destruction (tab. 8).

Tabel 8

Main differences between Chisinau, Balti and Cahul according to the characterstics of the patients

Factors Chisinau-Balti		Attributible risk (%)		
		Chisinau-Cahul	Balti-Cahul	
Demographics	Urban	N/appl	70,66	75,00
	Rural	N/appl	N/appl	85,71
Social features	Lack of insurance	28,00	N/appl	21,00
	Economical vulnerable state	26,30	N/appl	29,82
	Unemployment	N/appl	N/appl	17,51
	Homelessness	N/appl	75,98	N/appl
Biological features	Co-morbid state	49,47	68,29	83,97
	Chronic alcoholism	74,81	N/appl	79,54
Case-management	Detected by GP	37,06	N/appl	21,39
	Direct addressing to the hospital	29,48	28,87	N/appl
Microbiological features	GeneXpert Rifampicin sensible	26,83	N/appl	N/appl
	GeneXpert Rifampicin resistant	21,32	N/appl	N/appl
Radiological features	Extensive TB in 2 lungs	69,79	N/appl	56,99
	Lung destruction	N/appl	22,71	N/appl
Outcome	Treatment success	25,98	28,09	N/appl

Note: N/appl -non applicable.

Discussion

Summarizing the data it can be concluded that the Republic of Moldova showed a continuous decreasing of the long-term growth determinants according to the Global Competitiveness Report. It is evaluated as a country at the first stage of the economic development placed among the 35 poorest countries in the world. Tuberculosis burden placed the country on the 104th place with a financial impact of the disease on the economy – on the 88th place.

Low public financing contributed to the poor screening of high risk and hard-to-reach groups, deficiency in performing the effective anti-tuberculosis treatment and lack of interventions to resolve social and economical patients' problems.

Official statistical data established the decrease of the general population of the Republic of Moldova, increase of the urban population and the mortality rate. The obtained results proved that the inequalities are due to poor distribution of the financial resources for the public health care.

The uninsured part of the Moldovan population ranged from 20.3% to 24.5% (30% in the rural areas in 2008). Lack of the health care insurance contributed to the polarization of the health care services, low medical coverage of the high risk groups, deficient active screening and poor public health care control.

Although it was established a decreasing vectors of main tuberculosis epidemiological indices (incidence, prevalence and mortality) the epidemiological state of tuberculosis in the Republic of Moldova remains endangered.

Conclusions

Attributable risk identified the main disparities between Moldovan regions. In the Chisinau group compared to the Balti group predominated patients in economical vulnerable state, without health insurance, GeneXpert MTB/ Rifampicin sensible and those that finished the treatment with success. In the Balti group predominated chronic alcohol abusers or patients diagnosed with chronic alcoholism, co-morbid patients, severe pulmonary tuberculosis, patients addressed to the hospital due to broncho-pulmonary signs, infection with GeneXpert MTB/Rifampicin resistant strains of *Mycobacteria*.

The major differences between patients from the Chisinau and Cahul groups, with predominance in the Chisinau group were: homeless, co-morbid patients and those that succesfully finished the treatment and in Cahul - rural residence, direct addressing to the regional hospital and severe tuberculosis. The differences between patients from the Balti and Cahul groups, with predominance in the Cahul group were: rural residence, economical vulnerable state and patient's detection by general practitioner. On the other hand in the Balti group predominated co-morbid patients, alcohol abusers or diagnosed with chronic alcoholism, patients with severe extensive tuberculosis complicated with lung destruction.

For reducing the impact of tuberculosis as a factor contributing to the country's low health care standards, there were recommended several measures, such as: social assistance of vulnerable groups, improvement of the general public life style, reducing the harmful habits (tobacco smoking, alcohol use and illicit drug use) and improvement of the community conditions.

Tuberculosis defined as a social-related disease associated with the defects in social organization needs implementation of the well established priority interventions included in new sustainable development goals.

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Mortality through associated illnesses in tuberculosis patients and post-mortem pulmonary tuberculosis diagnosis in Chisinau

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Abstract

Background: The main cause of death of tuberculosis patients is the progression of tuberculosis, but the presence of associated diseases decreases the outcome of treatment of both the underlying and the associated disease, and the latter is the cause of death. Thus, reducing the mortality of tuberculosis patients can be solved by increasing the therapeutic success rate of tuberculosis as well as associated diseases.
Material and methods: A selective, descriptive and retrospective study was carried out in 3 time periods: period I (2001-2003) – implementation of the DOTS strategy in Chisinau municipality; period II (2007-2009) characterized by the tense epidemiological situation, the high TB mortality indicator and the implementation of the STOP TB strategy; period III (2013-2015) characterized by a shift to "End TB" strategy and a marked decrease in tuberculosis mortality.
Results: Analyzing the reference periods, we found that in the 1st period 1/4 of the total deaths were caused by tuberculosis, associated diseases and other causes, in the 2nd period there was a decrease in the number of deaths, and in the 3rd period there was about 2 times increase in the number of deaths.
Conclusions: The most common concomitant diseases were: oncological, cardiovascular, hepatic cirrhosis and other causes. The number of deaths with the post-mortem tuberculosis diagnosis was decreasing; half of them occurred at home, ½ of the deceased were without a stable place of living.
Key words: Associated pathologies, mortality, post-mortem.

Introduction

Tuberculosis (TB) remains one of the ten leading causes of mortality and is the second most common cause of infectious diseases worldwide after HIV/AIDS. The problem of TB mortality decrease is of a planetary nature [3]. According to World Health Organization (WHO) the TB mortality rate decreased worldwide by 47% between 1990 and 2015. It is estimated that 49 million lives were saved by diagnosing and treating tuberculosis between 2000 and 2014 [8, 22].

The twentieth century has been marked by a revolution in the field of fetal care with the emergence of the BCG vaccine and the first and second-line anti-tuberculosis drugs. These implementations in practice have allowed the spectacular decrease in disease frequency in developed countries over a long period of time, creating the impression that the disease will be defeated [8, 23, 24]. However, since the 1990s, the worsening of the socio-economic situation, together with the imbalance in the health care system, has contributed to the worsening epidemiological indexes [25, 27, 28, 29].

The indicator of tuberculosis mortality is one of the most important demographic indicators. It characterizes not only the demographic well-being of the population but social and medical, as well [14, 16, 18]. Between 1990 and 2015 there was an essential decline in the 47% mortality rate worldwide [3, 10, 13, 24]. The index of tuberculosis morbidity after 1990 in the Republic of Moldova has increased by 3-4 times, but in recent years it has stabilized and even decreased to 10 per 100.000 population in 2015 and in 2016 constituted 11 per 100.000 population [5, 13, 15]. In Chisinau, the mortality index registered a proportion of 6,8 per 100.000 thousand population with a decrease by approximately 50% between 1990 and 2015 [9, 10, 11]. WHO for the years 2016-2035 recommends a reduction in mortality by 90% compared to 2015. The National Program for TB Control in the Republic of Moldova for the years 2016-2020 predicts a mortality decrease by 35% [3].

The main cause of death of tuberculosis patients is the progression of tuberculosis, but the presence of associated diseases decreases the outcome of treatment of both the underlying and the associated disease, and the latter is the cause of death [1, 6]. Thus, reducing the mortality of tuberculosis patients can be solved by increasing the therapeutic success rate of tuberculosis as well as associated diseases [19, 20, 26, 28]. Post-mortem diagnosis of tuberculosis varies between 2.0 and 6.0% of new cases of TB in different countries [7, 12, 17, 21]. The veracity of the mortality rate in tuberculosis, despite the high level of informality, largely depends on the expertise quality of the cause of death [2]. Of particular importance in this context is the incorrect interpretation by the morphopathologist or forensic expert of the pathomorphological picture of tuberculosis, especially in post-mortem established diagnosis [23]. The level of post-mortem diagnosis has a decreasing trend lately. Errors in the diagnosis of tuberculosis are possible among the cases of post-mortem TB deaths in patients with acute forms of acute and epidemiological tuberculosis, predominantly in people living with HIV [26]. Cases of death with post-mortem diagnosis of TB reflect the level of detection organization, the quality of diagnosis of tuberculosis and occur more frequently in people without a stable place of living, diagnosis being determined by legal medicine or somatic stations [21].

Literature data on the causes of mortality of tuberculosis patients through concomitant diseases are contradictory. Associated diseases are recorded in one third of tuberculosis patients [28]. According to some data presented in the year 2014 tuberculosis patients on the record died due to other diseases and causes in 53.6% cases [28]. The rate of tuberculosis patients who died of HIV infection reached 23.4%

in the year 2010 [26]. The post-mortem diagnosis of TB increases the mortality index in different territories.

Thus, in the mortality structure the causes of death are the result of multifactorial action on the human body, and among the main ones both the worsening of social-economic conditions and the level of organization of the service of pneumophtiziology are emphasized.

The purpose of the study was the comparative analysis of the cases of TB patients with other diseases and causes and the evaluation of post-mortem TB diagnosis among the new cases in Chisinau in three periods of time.

Material and methods

A selective and discursive retrospective study was carried out in 3 periods of time: period I (2001-2003) - Implementation of the DOTS strategy in Chisinau; period II (2007-2009) characterized by the tense epidemiological situation, the high TB mortality indicator and the implementation of the "STOP TB" strategy; period III (2013-2015) characterized by a shift to "End TB" strategy and a marked decrease in tuberculosis mortality.

For the purpose of the research, the cases of TB deceased patients in Chisinau with post-mortem diagnosis were studied in three periods of time: during the first period in Chisinau, 494 patients died of tuberculosis and the diagnosis of post-mortem TB was established in 99 (20± 1.8%) patients; in period II of the total 456 deaths of tuberculosis, 63 (13.8± 1.6%) cases were detected post-mortem; in the third period of the total 225 deaths from tuberculosis, 29 (12.9±2.2%) cases were detected post-mortem. Also, from the total number of deaths from tuberculosis in Chisinau in the reference periods were selected the cases of patients with pulmonary tuberculosis deceased of associated diseases and other causes: 157 (25.3%) cases were selected in period I, in the period II – 110 (19.5%) cases and in period III – 112 (33.5%) cases.

Results and discussion

Analyzing the reference periods, we found that tuberculosis, associated diseases and other causes in the first period led to 1/4 of the total deaths, in the second period there was a decrease in the number of deaths, and in the third period there was an approximately twice increase in the number of deaths.

Table 1

Distribution by gender

Sex	Period I (2001-2003) n=157		Period II (2007-2009) n=110		Period III (2013-2015) n=112	
	No	M±m%	No	M±m%	No	M±m%
Men	121	77.1±3.4	79	71.8±4.3	89	79.5±3.8
Women	36	22.9±3.4	31	28.2±4.3	23	20.5±3.8

Note: no statistically significant difference between the periods has been established, p>0.05.

Analyzing the distribution of patients by gender, we established the significant predominance of male individuals versus female subjects in all periods studied (p<0.05). The male/female ratio was 3.4/1 in the first period, 2.5/1 in the second period and 3.8/1 – in the third period. Differences between the studied periods were not significant. The breakdown of cases by gender is shown in table 1.

The distribution of deaths by age showed that in the 0-4 age group, deaths were recorded only in period I (1.3±0.8%) and in period II (0.9±0.9%). In the age group 15-24 years, the number of deaths was low: 3.2±1.4% of cases in the 1st period, 0.9±0.9% of cases in the 2nd period and 0.9±0.8% in the 3rd period, and in the age group 25-34 years: 10.8±2.4%, 13.6±3.2% and 10.7±2.9% of cases, respectively. Deaths predominated in working-age patients (35-64 years) and the distribution was similar in the studied periods: 70.9% and 69.6% respectively. In the 35-44 age group the number of deaths predominated significantly in period I versus period II, for other age groups the differences between the reference periods were not significant. In the group of patients aged 65 years and over, the number of deaths increased insignificantly: 14.7±2.8%; 13.7±3.2%; 18.8±18.7% of cases, respectively. Data are reflected in table 2.

Table 2

Distribution of cases by age

Age	Period I (2001-2003) n=157		Period II (2007-2009) n=110		Period III (2013-2015) n=112	
	No	M±m%	No	M±m%	No	M±m%
0-4	2	1.3±0.8	1	0.9±0.9	0	0
15-24	5	3.2±1.4	1	0.9±0.9	1	0.9±0.8
25-34	17	10.8±2.4	15	13.6±3.2	12	10.7±2.9
35-44	41	26.1±3.5*	17	15.5±3.4	23	20.5±3.8
45-54	36	22.9±3.3	36	32.7±4.4	31	27.7±4.2
55-64	33	21.0±3.2	25	22.7±3.9	24	21.4±3.8
65+	23	14.7±2.8	15	13.7±3.2	21	18.8±18.7

Note: * – statistically significant difference between period I and II, p<0.05.

Studying the background of the deceased, we found the prevalence of urban people in all three studied periods (p<0.05): 86.6±2.7%, 75.5±4.1% and 54.4±4.4% of cases, respectively. During the analyzed periods, a significant increase in the number of deaths among persons in the suburbs was recorded in period II (24.5±4.1%) and III (33.0±4.4%) compared to period I (13. 4±2.7% of cases), p<0.05. The number of people living in the urban area predominated significantly in period III (12.5±3.1% of cases) compared to period II (4.5±1.9% of cases), p<0.05.

Analyzing the cases studied according to the methods of detecting the deceased, we established that the majority of patients in period I (98.7±0.8%) were detected by the passive method, by direct addressing. The dynamics shows a decrease in the direct addressing of patients to medical care: period II – 22.7±3.9% of cases and period III – 32.1±4.4% of cases, the differences compared to period I were of statistical

significance (p<0.05). The activity of the family physician is manifested in periods II and III, by the detection of symptoms, which accounted for 1/3 of the cases during periods II and III. The detection of patients by the prophylactic control (active method) was not insignificant and decreasing: in the second period – 14.5±3.3% of cases and in the third period – 8.9±2.6% of cases. The passive detection by addressing with the symptoms to other specialists was 1/5 of the deceased and the active detection was low: it is missing in period I; in period II – 8.1±2.6% of cases and in period III – 6.4±2.2% of cases. The data obtained are shown in table 3.

Table 3

Distribution of cases according to the detection method

Method	Period I (2001-2003) n=157		Period II (2007-2009) n=110		Period III (2013-2015) n=112	
	No	M±m%	No	M±m%	No	M±m%
Direct addressing	155	98.7±0.8	25	22.7±3.9*	36	32.1±4.4●
Symptomatic by family doctor	0	0	37	33.7±4.5*	36	32.1±4.4●
Prophylactic by family doctor	0	0	16	14.5±3.3*	10	8.9±2.6●
Symptomatic by another specialist	2	1.3±0.8	23	21.0±3.8*	23	20.5±3.8●
Prophylactic by another specialist	0	0	9	8.1±2.6*	7	6.4±2.2●

Note: * – statistically significant difference between period I and II, p<0.05;

The distribution of deaths by the type of case was the following: the new case was confirmed in the majority (82.2±3.0%) of the deceased patients in period I, in period II it decreased to 51.8±4.7% of cases and in period III – to 44.6±4.6% of cases. Relapses were recorded more frequently in periods II and III compared to period I: 28.2±4.2%, 31.3±4.3%, 12.1±2.6%, respectively. The other types of cases (lost to follow up, therapeutic failure, chronic case) varied between 1.3-6.3% of cases. The distribution according to the recorded case is shown in table 4.

Table 4

Distribution by the type of case

Type of case	Period I (2001-2003) n=157		Period II (2007-2009) n=110		Period III (2013-2015) n=112	
	No	M±m%	No	M±m%	No	M±m%
New case	129	82.2±3.0	57	51.8±4.7*	50	44.6±4.6●
Relapse	19	12.1±2.6	31	28.2±4.2*	35	31.3±4.3●
Lost to follow up	0	0	8	7.3±2.4*	16	14.3±3.3●
Therapeutic failure	0	0	11	10±2.8*	8	7.1±2.4●
Chronic case	0	0	2	1.8±1.2	3	2.7±1.5
Transferred	9	5.7±1.8	1	0.9±0.9*	0	0●

Note: * – statistically significant difference between period I and II, p<0.05;
● – *statistically* significant difference between period I and III, p<0.05.

Of the clinical-radiological forms, infiltrative pulmonary tuberculosis predominated significantly in all three periods (p<0.05): 73.2±3.5% in period I, 70.9±4.3% in period II and 88.4±3.0% of cases in period III, followed by disseminated form: 8.3±2.1%, 9.1±2.7%, 3.6±1.8%, respectively, and then fibrocystic tuberculosis: 5.1±1.7% of cases in period I and 10±2.8% of cases in period II and was not recorded in period III. Intravascular extracellular tuberculosis as well as different organs varied between 0.3-0.8% of cases. Distribution according to the clinical forms of tuberculosis is presented in table 5. Intrathoracic and various organs vary between 0.3-0.8% of cases.

Table 5

Distribution according to the clinical forms of tuberculosis

Form	Period I (2001-2003) n=157		Period II (2007-2009) n=110		Period III (2013-2015) n=112	
	No	M±m%	No	M±m%	No	M±m%
Primary TB Complex	0	0	1	0.9±0.9	0	0
ITLN TB	2	1.±0.8	1	0.9±0.9	0	0
Peripheral TB adenopathy	1	0.6±0.6	0	0	0	0
Infiltrative TB	115	73.3±3.5●	78	70.9±4.3◊	99	88.4±3.0
Nodular TB	2	1.3±0.8●	0	0◊	7	6.3±2.3
Fibro-cavitary TB	8	5.1±1.7●	11	10±2.8◊	0	0
Disseminated TB	13	8.3±2.1	10	9.1±2.7	4	3.6±1.8
TB pleurisy	10	6.4±1.9●	6	5.5±2.1◊	0	0
TB of the bronchi	1	0.6±0.6	0	0	0	0
TB of the spine	2	1.3±0.8	0	0	2	1.7±1.3
TB of other bone locations	1	0.6±0.6	1	0.9±0.9	0	0
Renal TB (160)	1	0.6±0.6	0	0	0	0
TB of other organs	1	0.6±0.6	0	0	0	0
TB of CNS	0	0	2	1.8±1.2	0	0

Note: ITLN – intrathoracic lymph node, CNS – central nervous system,
● – statistically significant difference between period I and III, p<0.05;
◊ – statistically significant difference between IInd period and IIIrd period, p<0.05.

Respectively, the study of the results of the microscopic sputum examination at BAAR revealed a large number of deceased persons with the negative result in all periods: 59.2%; 47.3%; 55.4% of cases. Respectively, the results of MBT's cultural exams show even lower scores, increasing over the past periods: 17.2±3.0%, 30.0±4.3%, 43.7±4.6%. Absent dates on the bacteriological examination were evidenced in the Ist period at 53.4±3.9% of cases with a significant decrease in the 2nd period (12.8±3.1%) and in period III (14.3±3.3% of cases). The results of MBT sensitivity tests on anti-tuberculosis drugs reported that the sensitivity of MBT to anti-tuberculosis drugs decreased markedly in dynamics in the three periods: 55.5%, 39.4%, 22.4% respectively, and the MBT resistance to anti-tuberculosis drugs increased respec-

tively in: 44.4%; 60.6% and 77.6% of cases. The results of the microbiological examination are presented in table 6.

Table 6

The results of the microbiological exam

MBT	Period I (2001-2003) n=157		Period II (2007-2009) n=110		Period III (2013-2015) n=112	
	No	M±m%	No	M±m%	No	M±m%
Positive	27	17.2±3.0*	33	30±4.3◊	49	43.7±4.6●
Negative	24	15.3±2.8*	35	31.8±4.4	42	37.5±4.5●
Missing data	91	57.9±3.9*	29	26.4±4.2	19	16.9±3.5●
It was not done	15	9.6±2.3	13	11.8±3.0◊	2	1.8±1.3●

Note: * – statistically significant difference between the Ist period and the 2nd period, p<0.05; ● – statistically significant difference between the Ist period and the 2nd period, p<0.05

Among cases with drug-resistant tuberculosis, multidrug resistance predominated in all periods studied with a higher frequency in the 3rd period. A similar number of patients was recorded with monoresistance, while the polyresistance was decreasing. The distribution of cases according to the spectrum of resistance is shown in table 7.

Table 7

The distribution of cases according to the spectrum of resistance

DST Results	Period I (2001-2003) n=12		Period II (2007-2009) n=20		Period III (2013-2015) n=38	
	No	M±m%	No	M±m%	No	M±m%
Mono	2	16.6±10.7	3	15±7.9	6	15.8±5.9
Poli	4	33.4±13.6●	3	15±7.9	2	5.3±3.6
MDR	6	50±14.4	14	70±10.2	30	78.9±6.6

Note: DST – drug susceptibility testing, ● – statistically significant difference between the 1st and the 3rd period, p<0.05.

Causes of death of tuberculosis patients by associated illness and other factors were broadly diverse and are reported in Table 8.The most common cause of death in all periods studied was oncological pathology (lung, head and neck, liver, prostate), followed by cardiovascular pathology (ischemic cardiopathy) and decompensated liver cirrhosis that were more frequently confirmed in period I, then more frequent community pneumonia in period II and chronic alcoholism predominantly in period III. Vascular attack followed the most frequent occurrence in period I, followed by HIV/AIDS and myocardial infarction more frequently in period II and diabetes.

Among other causes of death were: thromboembolism which was certified only in the 2nd and the 3rd period (1.8% and 2.7%, respectively) and renal insufficiency. Gastric ulcer was the cause of death only in period II (27%). Septicemia caused by other diseases was in 1.2%, 0.9%, 3.6% of cases, respectively. Other factors that caused death: road accidents (9.6%, 2.7%, 3.6%); suicide (0.6%, 1.8%, 0.9% of cases respectively); thermal combustion (0.6%) and frostbite (4.5%) were recorded only in the 1st period, and CO2 poisoning – only in the 2nd period (0.9%).

Table 8

Causes of death of tuberculosis patients by other diseases

The cause of death	Period I (2001-2003) n=157		Period II (2007-2009) n=110		Period III (2013-2015) n=112	
	No	M±m%	No	M±m%	No	M±m%
Oncological pathology	28	17.8±3.0	21	19.1±3.7	24	21.4±3.8
Pathology of the cardio-vascular system	32	20.4±3.2*	5	4.5±1.9◊	15	13.4±3,2
Decompensated liver cirrhosis	27	17.2±3.0	15	9.6±3.2	10	8.9±2.6●
Community pneumonia	7	4.5±1.6	5	4.5±1.9◊	15	13.4±3.2●
Chronic alcoholism	7	4.5±1.6	10	9.1±2.7	10	8.9±2.6
Cerebral ischemic attack	13	8.3±2.1	7	6.4±2.3	6	5.4±2.1
HIV AIDS	6	3.8±1.5*	15	13.6±3.2◊	3	2.7±1.5
Myocardial infarction	3	1.9±1.0*	9	8.2±2.6	5	4.5±1.9
Diabetes	7	4.5±1.6	5	4.5±1.9	3	2.7±1.5
Other causes	27	17.2±3.0	18	16.4±3.5	21	18.8±3.6

Note: * – statistically significant difference between period I and II, p<0.05. ◊ – statistically significant difference between IInd period and IIIrd period, p<0.05. The distribution of cases according to the place of death is reported in table 9.

Table 9

The place of death

The place of death	Period I (2001-2003) n=157		Period II (2007-2009) n=110		Period III (2013-2015) n=112	
	No	M±m%	No	M±m%	No	M±m%
At home	92	58.6±3.9*	45	40.9±4.6	39	34.8±4.5●
Somatic Hospital	34	21.7±3.2	20	18.2±3.6	29	25.9±4.1
Specialized hospital	21	13.3±2.7*	35	31.8±4.4	26	23.2±3.9●
Other places	10	6.4±1.9	10	9.1±2.7	18	16.1±3.4●

Note: * – statistically significant difference between I period and II, p<0.05; ● – statistically significant difference between I period and III, p<0.05.

Analyzing the place of death, we found that tuberculosis patients died significantly more frequently due to associated diseases at home in the Ist period (p<0.05), the rate being decreased in the 2nd and 3rd periods. In the specialized tuberculosis hospitals, the index varied from 13.3±2.7% to 31.8±4.4%, and in the somatic one died every 5th patient from the 1st and 2nd periods and each fourth – in the third

period. Approximately 10% of patients died in other places.

In the reference years of the total post-mortem TB patients, 191 (16.3±1.1%) cases were diagnosed. Analyzing the number of deceased, diagnosed post-mortem in the studied periods, we established that in the dynamics the number of TB cases diagnosed post-mortem was decreasing. Data on the number of deaths with post-mortem tuberculosis from the total TB deaths are shown in table 10.

Table 10

Distribution of TB cases established post-mortem according to the studied periods

Period of study	TB deaths n = 1175	Post-mortem diagnosed TB	
		No	M ± m
I (2001-2003)	494	99	20,0 ± 1,8▪
II (2007-2009)	456	63	13,8 ± 1,6
III (2013-2014)	225	29	12,9 ± 2,2●

Note: ▪ – statistically significant difference between Period I and II, p<0.05; ● – statistically significant difference between Period I and III, p<0.05.

Comparing the results obtained in different periods, we pointed out that the number of deaths of TB detected post-mortem predominated in period I compared to period II and period III (p<0.05).

Analyzing the number of post-mortem deaths among new cases of TB we have identified a continuous decrease in the number of deaths among the new cases: 2324 cases – in the first period, 2126 cases – in the second period, and 1518 cases – in the third period. The percentage of cases detected post-mortem among new cases in the 1st period amounted to 4.3%, in the 2nd period – 3% and in the 3rd period – 1.9%.

By distributing the cases of deceased by gender we established the significant predominance of male compared to female in all three time periods (p<0.05): in the 1st period – 85 (85.9±3.5%) of men and 14 (14.1±3.5%) women, in the 2nd period – 47 (74.6±5.4%) and 16 (25.4±5.5%) women and in the 3rd period – 25 (86.2±6.4%) men and 4 (13.8±6.4%) women. The male / female ratio was 6: 1 in period I, 2.9:1 in period II and 5.0:1 in period III. Differences between the studied periods were not significant. Data are reported in table 11.

Table 11

Distribution of post-mortem TB cases by gender

Sex	Periods of study					
	I (2001-2003) n = 99		II (2007-2009) n = 63		III (2013-2015) n =29	
	No	M ± m	No	M ± m	No	M ± m
Men	85	85,9 ± 3,5▪	47	74,6 ± 5,4▪	25	86,2 ± 6,4▪
Women	14	14,1 ± 3,5	16	25,4 ± 5,5	4	13,8 ± 6,4

Note: ▪ – statistically significant difference between men and women, p<0.05.

Studying the age groups of the TB deaths detected post-mortem we established that in the first period the number of deaths predominated significantly in the 51-60 age group – 42 (42.4±4.9%) cases, followed by the age group 41-50 years – 26 (26.3±4.4%), then by age group 31-40 years – 14 (14.1±3.5%) cases, age group older than 60 years – 9 (9.1±2.8%) cases, (p<0.05) and age group 21-30 years – 8 cases (8.1±2.7%). Data are shown in table 12.

Table 12

Distribution of post-mortem TB deaths by age

Age groups years	Periods of study					
	I (2001-2003) n = 99		II (2007-2009) n = 63		III (2013-2015) n =29	
	No	M ± m	No	M ± m	No	M ± m
21-30	8	8,1±2,7	2	3,2 ±2,2	5	17,2±7,0*
31-40	14	14,1 ± 3,5	12	19,1±4,9	5	17,2 ±7,0
41-50	26	26,3±4,4	19	30,1 ±5,7	5	17,5 ±7,0
51-60	42	42,4±4,9	19	30,1±5,7	5	17,5 ±7,0 ▪
≥60	9	9,1± 2,8	11	17,5±4,7	9	31,0 ±8,5▪

Note: ▪ – statistically significant difference between period I and period III, p<0.05; ● – statistically significant difference between period II and period III, p<0.05.

In the second period, 41-50 years old age group and the 51-60 age group had a similar number of TB deaths – 19 (30.1±5.7%) cases, which predominated insignificantly from the group aged 31-40 years – 12 (19.1±4.9%) cases and the age group older than 60 years – 11 (17.5 ±4.7%) cases and significantly compared with the age group 21-30 years - 2 (3.2±2.2%) cases, (p<0.05). In period III in the 21-30 years, 31-40 years, 41-50 years and 51-60 years, 5 cases (17.5±7.0%) were recorded post-mortem, and in the age group older than 60 years – 9 (31.0±8.5%) cases. Comparing the studied periods, we pointed out that the deaths in the age group 51-60 predominated significantly in period I compared to period III (p<0.05), in the age group over 60 years deaths predominated in period III compared to period I (p<0.05) and in the age group 21-30 deaths predominated in period III compared to period II (p<0.05).

Table 13

TB deaths detected post-mortem according to the place of death

Periods of study	The place of death					
	Home		Somatic hospitals		Other places	
	No	M ± m	No	M ± m	No	M ± m
I (2001-2003), n = 99	50	50,5±5,0	23	23,2±4,2	26	26,3±4,4
II (2007-2009), n = 63	28	44,4±6,2	9	14,3±4,4	26	41,3±6,2 ▪
III (2013-2015), n = 29	15	51,7±9,2	9	31,0±8,5	5	17,3±7,0 *

Note: * – statistically significant difference between period III and II, p<0.05; ▪ – statistically significant difference between period II and I, p<0.05.

Analyzing the place of death, we established that in all three periods approximately 1/2 of the patients died at home: in period I – 50 patients (50.5±5.0%), in period II – 28 (44.4±6.2%) patients and in period III – 15 (51.7±9.2)

cases. In somatic hospitals died: in period I –23 patients (23.2±4.2%), in period II – 9 (14.3±4.4%) patients and in period III – 9 (31.7±8.5%) cases. In other places, died: in the 1st and 2nd periods – 26 patients (26.2±4.4% and 41.3±6.2% respectively) and in the 3rd period – 5 (17.3±7.0 %) cases, significantly less compared to period II, ($p<0.05$). Data are presented in table 13.

By evaluating the belonging to socially vulnerable groups, we established that among the cases of deaths with post-mortem TB 44 (44.4±4.9%) patients in period I, 26 (41.3±6.2%) patients in period II and 9 (31.0±8.6%) patients in period III were without stable living space (homeless). The distribution of TB deaths detected post-mortem according to the presence/absence of the place of residence is shown in figure 1.

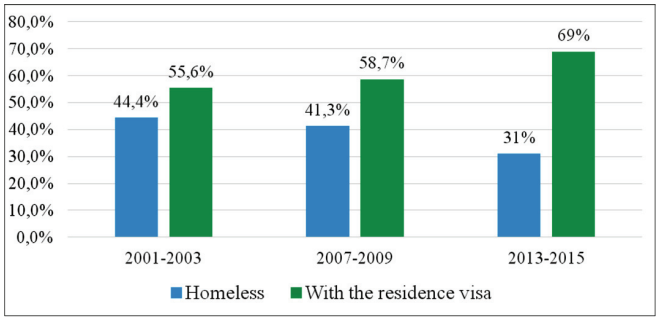

Fig. 1. Distribution of TB deaths detected post-mortem.

Thus, during the studied periods, we have determined the decrease of the number of patients' living places. This was done with the help of the non-governmental organization "AFI" through the early active detection of tuberculosis and the treatment in both phases in stationary conditions.

Conclusions

The number of deaths of pulmonary tuberculosis due to concomitant illnesses and other causes in the reference periods was rising as the number of deceased persons in suburbs increased. Male subjects predominated compared to females both in the group of deaths from pulmonary tuberculosis due to concomitant diseases and in post-mortem diagnosis of tuberculosis. Detection of deaths of tuberculosis patients by progression of associated diseases was predominantly realized by the passive method, with the predominance of pulmonary tuberculosis, with a high rate of infiltrative form in the tuberculosis process destruction phase in approximately half of cases.

Sputum microscopy at BAAR was negative in half of the deceased, during the last two periods the number of bacteriological examinations increased; the increase of MBT resistance to anti-tuberculosis drugs took place on the account of MDR resistance. Associated diseases that more frequently contributed to the death of the tuberculosis patient are: cancer of various organs, ischemic heart disease, cirrhosis, community pneumonia, alcoholism and other causes.

The number of deaths with post-mortem diagnosis of tuberculosis and their share among new cases has been decreasing in the studied periods. Half of the deaths with the post-mortem diagnosis of tuberculosis occurred at home, their number being stable in all studied periods, the number of deaths in the somatic stations increased during the third period, and the deaths in other places doubled during the period II and have been decreasing in the third period.

Approximately 1/2 of deceased individuals with post-mortem diagnosis of tuberculosis had no place of stable living, but there is a downward trend in the number of homeless deceased in the 3rd period.

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Coffee consumption influence upon the clinico-neurophysiological manifestations of primary sleep bruxism

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Abstract

Background: Caffeine is one of the most widely-used psychoactive substances, having multiple stimulating effects. Caffeine is being considered as eliciting a dose-dependent effect on sleep bruxism.

Material and methods: There were investigated 100 patients with primary sleep bruxism. Patients were clinically examined, there were given several questionnaires, and they underwent a series of investigations: sleep bruxism recording; surface electromyography, occlusal reflex determination, jc.SSR (*jaw clenching sympathetic skin response*) recording and masseter muscle ultrasonography.

Results: In patients with primary sleep bruxism, there were observed various coffee intake patterns/24 h: "abstinent" group – 32%; "1-3 cups" group – 38.1%; "4-6 cups" group – 19%; ">6 cups" group – 11%. People who consume >6 cups/24 h, have increased the number of nocturnal clenches. Pathological occlusal reflex indices were observed in the "1-3 cups" group (76.3%), "4-6 cups" group (89.5%), ">6 cups" (100% cases), "abstinent" group (50%). Disorders associated with the temporomandibular joint and the bruxism-associated pain reach pathological values in individuals who consume 4-6 or more cups of coffee. Excessive caffeine consumption leads to the increase of the amplitude of the sympathetic autonomous potential (jc.SSR, A2, mV) without significant changes in the central autonomous regulation time (jc.SSR, T, s).

Conclusions: There were observed various coffee intake patterns in patients with primary sleep bruxism. Excessive coffee consumption is associated with the stress level. The masseter muscle thickness and dental wear show no statistically significant elevation trends, under the influence of various caffeine doses.

Key words: sleep bruxism, caffeine, clinical-neurophysiological indices.

Introduction

Caffeine is widely-used on a daily basis, being a psychoactive substance with multiple stimulating effects – it reduces the total duration of sleep, changes the pattern and the quality of night sleep, increases the wakefulness level and the information processing speed, modifies the activity of the cortico-cerebral neurons and influences the psycho-emotional status [22, 24].

It has been assumed that caffeine has a dose-dependent effect on sleep bruxism [24]. Caffeine consumption and the incidence of bruxism do not differ essentially based on the gender of the individuals, thus coffee consumption in males reaches the following levels: 3-8 cups – 3.8%; more than 8 cups – 7.5%; respectively in women: 0-3 cups – 4.6%; 3-8 cups – 3.9%; more than 9 cups – 5.9% [24]. Svenson et al. [29] have highlighted the dangerous threshold for the onset/maintenance of sleep bruxism – caffeine consumption of more than 6 cups per day. Increased caffeine consumption has been shown to increase the severity of sleep bruxism [17], and the consumption of 6 and more cups of coffee per day increases the risk of sleep bruxism by 1.4 times [21]. However, in other investigations, these data have not been confirmed [1]. Caffeine stimulates the masticatory muscles [8], it increases the subjective sensations pertaining to muscle tension, along with an increase in anxiety tendencies – representing typical signs of sleep bruxism [22]. Bastien et al. [3] have conducted a study on the bioelectric activity of the masseter muscles in patients with sleep bruxism under the action of caffeine and did not detect any significant differences in comparison to the placebo group.

A slightly less studied aspect is the role of the autonomous nervous system in the pathogenesis of primary sleep bruxism. Under the influence of coffee, the sympathetic muscular activity increases by 54.1%, but the studied problem becomes even more complex in light of investigations, according to which the administration of caffeine-free coffee also causes the essential increase in sympathetic muscle activity [6].

Currently, there are no known factors that contribute to the worsening or maintenance of bruxism-associated disorders under the influence of caffeine, and there are not known the clinico-neurophysiological indices that may be informative for the monitoring of patients with primary sleep bruxism with various patterns of coffee consumption (intake of various caffeine doses).

Material and methods

In the study, there were enrolled 100 people with primary sleep bruxism. All patients were investigated according to the modern diagnostic protocol regarding bruxism, by applying clinical and paraclinical dental exam procedures (anamnesis, dental examination with the identification of dental wear, palpation of the masticatory muscles, computed tomography, etc.). The assessment of the presence and the severity of the clinical disorders were achieved by applying specialized questionnaires [25, 31, 36]: the bruxism questionnaire; the Fonseca questionnaire; the multifactorial questionnaire of bruxism-associated pain; the emotional stress questionnaire; the sleep questionnaire; the questionnaire regarding professions. For the quantitative assessment of emotional stress, we have applied the visual analogue scale (VAS). The division of

the stresogenic professions, was performed according to the criteria proposed by Nishimura [20].

We have assessed the degree of dental abrasion, according to the following grades: 0 – no abrasion; 1 – dental abrasion within the enamel boundaries; 2 - dental abrasion with a <1/3 crown destruction; 3 – dental abrasion with a >1/3 crown destruction [25].

In order to record the *total number of clenches* (TNC) and the *total clench time* (TCT), we have applied the SleepGuard SG5 portable device (Holistic Technologies Inc., USA). The investigation of the occlusal reflex (masseter inhibitory reflex), has been conducted according to the method developed by Tzvetanov et al. [32], with the application of the Neuro-MVP-micro diagnostic complex (Neurosoft). After recording the electromyogram, the analysis was performed based on the presence/absence of the *muscle silence period* SP2 with the latency of 40-60 ms and the minimum duration of 20 ms. Normal SP2 is highlighted as Type I, partially inhibited SP2 is classified as type 2 (EMG amplitude is 20 to 80% of the initial amplitude) and SP2 – Type 3 is considered to be the one without essential changes in the EMG amplitude.

The evoked autonomous potentials during jaw clenches (*jaw clenching sympathetic skin response* – jc.SSR) were recorded using the multifunctional computerized complex Neuro-MVP-micro (Neurosoft). We have analyzed the amplitude (A_2, mV) and the recovery period back to the initial levels (T, s) of the autonomous-sympathetic potential, evoked at the standardized maximum jaw engagement using cotton rolls as an interface in the region of premolars/molars (autonomous evoked potentials under standardized conditions).

The thickness of the masseter muscles has been determined by using the Envisor C device (Philips) and a 7.5 MHz linear transducer [10]. We have determined the thickness gradient for the masseter muscle (GCM), under conditions of muscle relaxation-maximum jaw clenching, based on the formula [11]: GCM = (Ga-Gr/Ga)*100%, where: Gr – the thickness of the masseter muscle (mm) during relaxation; Ga – the thickness of the masseter muscle during maximum jaw engagement. In healthy people, GGM is equal to 25%. The echostructure of the masseter muscle was determined by the analysis of the local and diffuse echogenetic features: normal echogenicity in the projection of the masseter muscle – 0 points; local pathological echogenicity – 1 point; diffuse pathological echogenicity – 2 points. The echogenicity index in healthy individuals is 0.23±0.07 points.

The amount of caffeine consumed was evaluated according to the literature recommendations [24], based on the number of coffee cups consumed in 24 hours (the estimated caffeine content in a cup depends on the type of drink: soluble coffee – 61-70 mg; espresso coffee – 97-125 mg; cocoa – 10-17 mg; tea – 15-75 mg; hot chocolate – 30 mg).

Inclusion criteria used in the research: a positive clinical diagnosis of primary sleep bruxism, confirmed by the objective recording of sleep bruxism episodes; partial edentulism (no more than 1-3 teeth); age of patients – 18-50 years; presence of the patient consent for participating in the research; cooperating patients.

Exclusion criteria used in the research: age not in the established range; other clinical forms of bruxism (central nervous system disorders, epilepsy, parkinsonism, etc.); the presence of anomalies and inflammatory signs in the stomatognathic system; the presence of signs of organic damage with the decompensation of the masticatory muscles activity (a bioelectric activity of less than 30 mcV as recorded on EMG, during a state of relaxation); various acute and chronic diseases during the exacerbation period; parasitosis; alcoholism, drug addiction, toxicomania, mental illness; treatments with psychotropic, anticonvulsant or miorelaxant drugs; lack of the patient consent for participating in the research; non-cooperating patients.

The obtained results were processed with the statistical software package *Statistics for Windows*, v. 11.0 (StatSoft, Inc., USA).

Results

Of all the investigated patients (n = 100), in 32% of cases, caffeine is consumed sporadically ("abstinent" group), and in 68% of cases, there was observed a constant caffeine consumption trend: 38% – 1-3 cups of coffee; in 19% of cases – 4-6 cups of coffee and in 11% of cases – more than 6 cups. Caffeine consumption in patients with sleep bruxism is higher in young people, and with ageing, caffeine consumption decreases considerably – the correlation between age and consumption is negative and statistically significant (R_{xy} = -0.534, p <0.001).

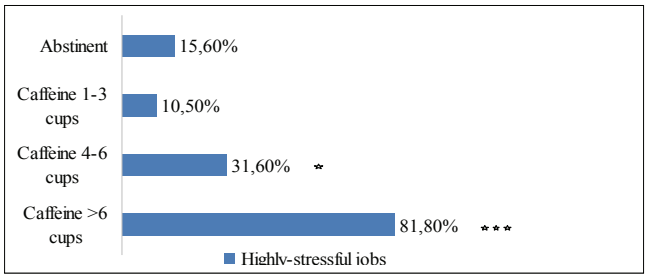

Fig. 1. Frequency of highly-stressful jobs vs. caffeine consumption per 24 hours in patients with primary sleep bruxism.

Note: statistical differences vs. "abstinent" group (* – p <0.05; *** – p <0.001).

Frequency of highly stressful jobs *vs.* caffeine consumption in patients with primary sleep bruxism: "abstinent" group – 15.6%, "1-3 cups" group – 10.5%, "4-6 cups" group – 31.6%, ">6 cups" group – 81.8 % (fig. 1).

The indices of emotional stress *vs.* caffeine consumption in patients with primary sleep bruxism are essentially different in relation to the caffeine dose. VAS-stress in the "abstinent" group is 4.8 ± 0.31 pt, in patients who consume 1-3 cups of coffee – 5.2 ± 0.33 pt, in patients who consume 4-6 cups of coffee – 6.1 ± 0.32pt, in patients who consume more

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Table 1

Age of patients with primary sleep bruxism, clinical manifestations of bruxism, and the ultrasonographic indices of the masseter muscles *vs.* caffeine consumption per 24 hours

Indices	Caffeine consumption			
	Abstinent (n = 32)	1-3 cups (n = 38)	4-6 cups (n = 19)	>6 cups (n = 11)
Age, years	37.1 ± 1.42	34.4 ± 0.98	32.6 ± 0.92*	28.5 ± 1.12***
Bruxism questionnaire, pt.	3.9 ± 0.25	4.8 ± 0.28*	4.9 ± 0.33*	5.9 ± 0.31***
Pain questionnaire, pt.	4.11 ± 0.51	4.40 ± 0.43	4.43 ± 0.42	5.90 ± 0.33*
Fonseca questionnaire, pt.	41.32 ± 3.66	48.39 ± 4.01	56.43 ± 3.96**	61.94 ± 4.15***
USG, GGM index, %	27.8 ± 0.48	28.0 ± 0.49	28.7 ± 0.51	29.0 ± 0.52
USG, echogenicity, un.	1.28 ± 0.10	1.30 ± 0.09	1.39 ± 0.10	1.43 ± 0.11
Dental wear, un	1.71 ± 0.24	1.79 ± 0.23	2.12 ± 0.18	2.13 ± 0.15

Note: statistical differences vs. "abstinent" group (* – p <0.05; ** – p <0.01; *** – p <0.001).

than 6 cups – 6.7 ± 0.23 pt. There were observed statistical significant differences in comparison with the "abstinent" group in the group of patients that consume 4-6 cups of coffee per 24 hours (p <0.01) and in the group with a consumption of more than 6 cups/24 h (p <0.001).

Based on the self-assessment data, pathological sleep in caffeine-abstinent patients was found only in 12.5% of cases (4 patients out of 32); a minimal degree of caffeine consumption (1-3 cups) leads to pathological sleep in 5 patients out of the 38 investigated (13.2%); a moderate coffee consumption (4-6 cups) is associated with the presence of pathological sleep in 63.2% of cases (12 patients out of the 19 investigated) and an excessive caffeine consumption is followed by sleep quality disturbance in 81.8% (9 out of the 11 patients investigated). In comparison to the caffeine-abstinent patients, statistically significant differences were observed for cases with a caffeine consumption of 4-6 cups and more of coffee (p <0.001). The duration of night sleep tends to decrease, but the differences between the investigated groups are insignificant: "abstinent" group – 7.6 ± 0.58 hours; "1-3 cups" group – 7.5 ± 0.53 hours; "4-6 cups" group – 6.8 ± 0.51 hours; ">6 cups" groups – 6.2 ± 0.45 hours.

Clinical manifestations of sleep bruxism, as assessed on the data collected from the clinical questionnaires, have shown certain peculiarities. An integral assessment (bruxism questionnaire) revealed a worsening of symptoms regardless of the caffeine dose, with a more pronounced increase in individuals that consume 6 cups of coffee per 24 hours (Table 1). The values of bruxism-associated pain reach statistical significance (p <0.05) in individuals that consume more than 6 cups of coffee per day. Temporomandibular joint-associated disorders (Fonseca questionnaire) reach statistically significant pathological values in individuals that consume 4-6 cups of coffee and are further aggravated by increasing the caffeine dose.

Another situation can be observed after the analysis of the GGM index and the echogenicity of the masseter muscles during the consumption of various doses of caffeine – pathological trends can be observed without reaching any statistically significant values (Table 1). Likewise, in the case of dental wear – there were not found any statistically significant values in all the groups that were investigated, based on the dose of consumed caffeine. The correlation coefficient between dental wear and caffeine consumption is 0.238 (p> 0.05).

The manifestations of the episodes of sleep bruxism (TNC, TCT) were also more pronounced in younger people who consumed more caffeine (fig. 2).

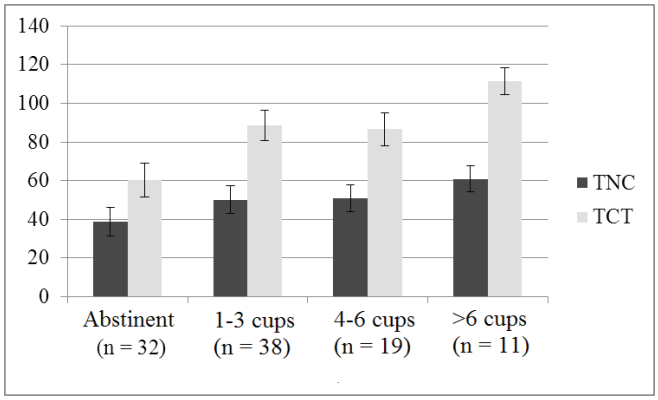

Fig. 2. Quantitative indices of bruxism *vs.* consumption of caffeine per 24 hours in patients with primary sleep bruxism.

Note: vertically – the total number of clenches (TNC, un.) and their total duration (TCT, s); statistical differences vs. "abstinent" group (* – p <0.05; *** – p <0.001).

TNC Index *vs.* caffeine consumption in patients with primary sleep bruxism: "abstinent" group – 38.7 ± 7.29 un., "1-3 cups" group – 50.1 ± 7.14 un., "4-6 cups" group – 50.8 ± 6.88 un., ">6 cups" group – 60.9 ± 6.63 un. TCT Index *vs.* caffeine consumption in patients with primary sleep bruxism: "abstinent" group – 60.37 ± 8.63 s, "1-3 cups" group – 88.67 ± 7.91 s, "4-6 cups" group – 86.61 ± 8.55 s, ">6 cups" group – 111.45 ± 6.89 s.

Caffeine influences the *occlusal reflex* index, depending on the amount consumed. In people who do not consume caffeine (abstinent), SP2 has a normal inhibition in 16 patients (50%), the other 16 patients (50%) have pathological inhibition. Regular consumption of 1-3 cups of coffee per day leads to pathological disruptions of the SP2 activity in 29 patients (76.3%, p <0.05 as compared to the "abstinent"

group), consumption of 4-6 cups causes pathological disorders of the SP2 inhibition processes in 16 patients (89.5%, p <0.01) and excessive coffee consumption (more than 6 cups) has resulted in the presence of pathological variants of SP2 in all the patients from that group (100%, p <0.001).

Table 2

Indices of autonomous-sympathetic manifestations in the stomatognathic system *vs.* caffeine consumption per 24 hours in patients with primary sleep bruxism

jc.SSR Indices	Caffeine consumption			
	Abstinent (n=32)	1-3 cups (n=38)	4-6 cups (n = 19)	>6 cups (n = 11)
jc.SSR, A_2, mV	2,15 ± 0,26	2,73 ± 0,22	2,82 ± 0,34	3,5 ± 0,38**
jc.SSR, T, s	9,8 ± 0,31	10,0 ± 0,36	9,9 ± 0,35	10,1 ± 0,34

Note: statistical differences vs. "abstinent" group (** – p <0.01).

In our investigations for the first time, it was shown that excessive caffeine consumption (more than 6 cups per day) leads to disturbances in the sympathetic autonomous activity in the stomathognathic system (jc.SSR, A_2, Table 2) without increasing the central regulation time (jc.SSR, T, s) in the processes of autonomous regulation.

Discussion

Considering that in the pathogenesis of sleep bruxism, the dysfunction of the cerebral structures takes the main place, it can be assumed that different psychoactive substances (alcohol, caffeine, etc.) can influence the central nervous system, eliciting an important effect on the pathogenetic mechanisms of sleep bruxism. Under day-to-day conditions, people use different psychoactive substances to achieve effects of relaxation, pleasure, or in order to relieve excessive stress or pain [13]. In this regard, we may conclude that sleep bruxism can be viewed as a disease associated with the states of psycho-emotional tension, with the high levels of anxiety and emotional stress, that may require the usage of psychoactive remedies [2, 24, 34, 35]. The analysis of literature data [3, 6, 8, 17, 21, 22, 24] and our own results, highlight a close link between the effects of caffeine and the manifestations of sleep bruxism.

We have established that the higher caffeine consumption in younger people correlates with more severe manifestations of sleep bruxism. Based on these data, it is difficult to establish the main cause – the young age or the excessive caffeine consumption. A recent study, based on questioning of a group of 113 students in Poland, did not reveal any statistically significant associations between coffee consumption and the incidence of bruxism [4].

The stressor psychosocial factors are in a close association with age, these play an important role, both in the pathogenesis of sleep bruxism and as well they influence the consumption degree for psychoactive substances [24]. Under conditions of chronic stress, muscular dysfunctions in the stomatognathic system occur in 34-46.2% of cases [28]. In our study, the presence of stresogenic professions is associated in 81.8% of cases with excessive caffeine consumption, and the manifestations of emotional stress (VAS-stress) are substantially higher at the consumption of 4 or more cups of coffee. The obtained results correlate with the ones from the scientific literature, according to which the effects of caffeine upon the psycho-emotional state are dose-dependent [26, 27].

Caffeine consumption has a pronounced effect not only on the psycho-emotional state but also on the sleep; caffeine consumption 16 hours before sleep, induces a much more superficial sleep [14]. We have determined that caffeine prolongs sleep latency, reduces the total sleep time and sleep efficiency, and the sleep quality is subjectively assessed as being a lower one. Caffeine consumption is associated with the *difficulty of staying asleep* (DSA) [15]. Our results have highlighted the interrelation between the dose of consumed caffeine and the quantitative/qualitative sleep disorders.

In the scientific literature, there are published researches which show that increased caffeine consumption, along with its negative influence upon the psycho-emotional status, as well on the duration and quality of sleep, increases the severity of sleep bruxism [17]. Our results prove that caffeine consumption, regardless of dose, increases the total duration of jaw clenches (TCT), but the consumption of more than 6 cups per day is the landmark dose that increases this index the most (TCT – 111.45 ± 6.89 s, p < 0.001). In comparison with the strong effect of caffeine on the TCT index, the changes of the total number of clenches (TNC) are less pronounced. In this context, it is important to mention the results obtained by Bastien et al. [3], which have shown that the bioelectric activity of the masseter muscle in patients with sleep bruxism under the influence of caffeine consumption did not change significantly when compared to placebo. Perhaps that caffeine mostly maintains and prolongs the pathological activity of masticatory muscles rather than it initiates new episodes of bruxism – this hypothesis is confirmed by the greater change in total clench time (TCT) in comparison with total number of clenches (TNC). In the scientific literature, there is a focus on the caffeine's ability of stimulating the masticatory muscles [8]. In recent years, there have been published several researches, analyzing the structural features of the masticatory muscles by applying ultrasonography. A normal ultrasonographic map of the masseter muscle is expressed by the presence of hyperecogenic strips parallel to the long axis of the muscle [10]. The obtained results show a trend towards increasing of the echogenicity of the masseter muscle that follows the increase in the amount of consumed caffeine, pathological changes occur in the muscles, fascia and connective tissues, expressed as local and/or diffuse changes in the echogenicity. The polymorphism of these changes that occur under the influence of excessive caffeine consumption, emphasizes the broad spectrum action of this psychoactive substance on the whole body and in particular, on the stomatognathic system.

The *feedback* connection between the occlusal contact

and the occlusal muscular force regulates the *occlusal reflex*, which is known in the scientific literature as the trigemino-trigeminal reflex, anti-nociceptive inhibitory reflex of the brain stem [15]. The first inhibitory phase of the occlusal reflex is determined by the inhibitory disinaptic neuronal network (inhibitory interleaving neurons, located in the trigeminal motor nucleus), and the second phase is determined by the inhibitory polysinaptic network (neurons located in the lateral reticulate formation at the level of ponto-medullary junction). These neural networks are strongly influenced by the activity of the limbic, cortical, cerebellar and hypothalamic structures [23, 33]. These modulating effects explain the variability of the occlusal reflex that was observed in our studies, based on the dose of consumed caffeine and the psycho-emotional state of the patients with primary sleep bruxism.

According to the scientific literature data, patients with bruxism did not reveal statistically significant correlations between EMG muscle activity during wakefulness/sleep and the degree of dental abrasion [9, 29]. As a result of the study, there was observed no valid correlation between dental wear and age of patients, between dental wear and occlusal factors, as well as in regard to the degree of temporomandibular joint dysfunction. These data prove that dental wear is associated to a large extent with extra-stomatognathic factors. According to the data from the literature, the presence of dental abrasion is not the main criterion for the diagnosis of sleep bruxism, because it may be found in other diseases as well (acid reflux, long-term consumption of acidic juices, etc.) [12, 19].

Caffeine has been shown to influence the activity of cortico-cerebral neurons and to strongly alter the psycho-emotional state, it increases anxiety and amplifies the subjective sensation of muscle tension [22]. There is evidence that the effects of caffeine are associated with the calcium release in the sarcoplasmic reticulum and the inhibition of its reabsorption, this being associated with the alteration of the neuromuscular function and with the increase in the muscle contracting force [30]. In recent years, the caffeine-emotions-bruxism interaction is studied based on the involvement of the adenosine neuromodulator, release of serotonin, acetylcholine, dopamine, etc. [16]. The obtained results indicate that the activity of the stomatognathic system is closely related to the processes of autonomous regulation, as highlighted by the jc.SSR method. The hypothalamus is the main generator of jc.SSR, and the modulation of the autonomous reaction is accomplished by several brain structures – the reticulate formation, the limbic system, etc. [37]. Under the influence of caffeine, we have established an increase of A_2, which is a sign of increased activity of ergotropic centers (sympathicotonia), but the central regulation time has not increased, which confirms the stimulating effects of caffeine.

The preventive results obtained in our studies, indicate that the analysis of caffeine effects on patients with primary sleep bruxism requires a multisystemic approach (Figure 3).

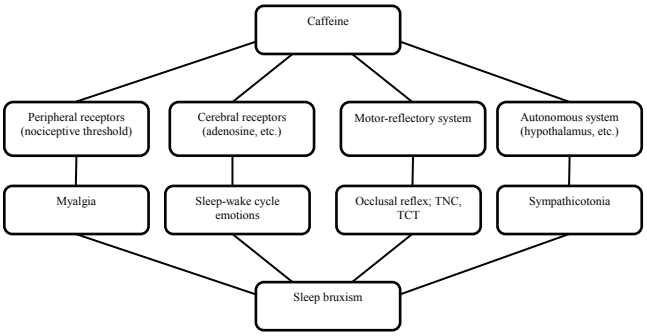

Fig. 3. Interaction scheme of caffeine effects and the manifestations of primary sleep bruxism.

Finally, we may conclude that the disorder expression degree under the action of caffeine depends not only on the amount of caffeine consumed, but also on the frequency of consumption, because the discontinuation of consumption leads to the occurrence of abstinence, which lasts up to 5 days – the period necessary for the readaptation of the adenosine sensitivity of the cerebral receptors [24]. During the abstinence periods, psychomotor and autonomous disorders worsen, significantly diminishing the quality and the duration of sleep. Patients with sleep bruxism, who consume excessively caffeine, are advised to gradually reduce the dose.

Conclusions

1. In patients with primary nocturnal bruxism, there were observed different patterns of caffeine consumption per 24 hours: "abstinent" group – 32.0%; "1-3 cups" group – 38.0%; "4-6 cups" group – 19.0%; ">6 cups" group – 11.0%. Caffeine consumption in patients with primary sleep bruxism decreases with ageing.

2. The presence of highly-stressful jobs, an increased level of emotional stress and hypersympathicotonia are associated with excessive caffeine consumption. Minimal caffeine consumption (1-3 cups) leads to pathological sleep in 13.8% of cases, and excessive consumption (>6 cups) is associated with pathological sleep in 81.8% of cases.

3. Caffeine intake, regardless of dose, increases the overall duration of night clenches, in comparison with a less pronounced effect on the total number of jaw clenches. A pathological occlusal reflex has been observed at the consumption of 1-3 cups of coffee in 76.3% of cases, in 89.5% of cases in the "4-6 cups" group, and in 100% of individuals from the ">6 cups" group; in the abstinent individuals – the occlusal reflex was pathological in 50% of cases.

4. The temporomandibular joint-associated disorders and the myogenic-algic manifestations, reach a significant value at the consumption of 4-6 or more cups of coffee, the thickness of the masseter muscle and dental wear exhibit no statistically significant tendencies of increase under the influence of different doses of caffeine.

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Determinants of loss to follow-up and tuberculosis patients' awareness

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Abstract

Background: The highest rate of patients with the low disease outcome is represented by the lost to follow-up and died cases. The aim of the study was to assess the major determinants of low tuberculosis treatment outcome.
Material and methods: A retrospective selective, descriptive, case-control study targeting social, demographic, economic and epidemiological peculiarities, case-management, radiological aspects and microbiological characteristics of 437 patients with pulmonary tuberculosis with different outcomes: cured and lost to follow-up was performed. Patients' awareness was established by performing a pre-designed schedule containing open-ended and close-ended questions, reflecting knowledge about disease. There were interviewed 151 patients treated after a previous lost to follow-up.
Results: It was established that the major risk factors for loss to follow-up were: the history of detention, migration, patients with MDR-TB, patient's addressing to the hospital, previous history of treatment and social vulnerability. Most of the patients were aware about the disease through the health personnel and were satisfied with the received knowledge. The proportion of those who were informed through the mass media was high. They knew that tuberculosis is curable with a complete treatment; however, every tenth considered that two-three months are sufficient.
Conclusions: Raising awareness among patients with high risks about the compliance and the duration of the treatment, emphasizing that the treatment is free of charge and will not be started after a previous drop up will improve disease outcome.

Key words: tuberculosis, risk factors, loss to follow up.

Introduction

Tuberculosis represents a major global health problem, well recognized in the Republic of Moldova (MD) [1]. According to the WHO report in 2015, 10.4 million new cases were reported worldwide, of which 5,9 million (56%) were among men, 5.5 million (34%) among women and 1.0 million (10%) among children. Among all new tuberculosis cases, 1.2 million (11%) were people living with HIV infection. Two thirds of all cases were living in 6 countries: India, Indonesia, China, Nigeria, Pakistan and South Africa [17]. In the Republic of Moldova 4.211 cases were notified in 2015, 3.608 were new cases, 85% of them were tested by rapid diagnostic methods, 95% had known HIV status, 90% had pulmonary tuberculosis and 64% were bacteriological confirmed [1].

The national implementation of the DOT (Directly Observed Treatment) strategy in the tuberculosis patient's management determined the epidemic extension of primary drug-resistant infection in the population (2005 – 13%, 2006 – 19%, 2007 – 18%, 2008 – 24%, 2009 – 22%, 2010 –25%, 2011 –26%, 2012 – 24%, 2013 – 25%, 2014 –25% from the total registered MDR-TB cases) that in consequence contributed to the reduction of treatment effectiveness (2005 – 62%, 2006 – 62%, 2007 – 62%, 2008 – 58%, 2009 – 57%, 2010 –52%, 2011 –62%, 2012 – 62%, 2013 – 62%) which was the lowest among the European region countries and lower in average by 20% compared with targeted 85% recommended by the WHO [1]. The low success rate was directly linked with the high rate of lost to follow-up patients: 2001-5.5%, 2002-15.6%, 2003-10.5%, 2004-10.4%, 2005-10.9%, 2006-11.7%, 2007-10.7%, 2008-7.4%, 2009-6.2%, 2010-7.9%, 2011-7.7%, 2012 – 5.2% [1].

The standard treatment for new drug-susceptible tuberculosis, according to WHO recommendations in MD is used since 2000 as a part of DOT strategy and lasts 6 months in new cases and 8 months in previously treated cases. The treatment of the new drug-susceptible patients consists in a two phase regimen with four first-line anti-tuberculosis drugs [isoniazid (H), rifampicine (R), ethambutol (E) and pyrazinamide (Z)] in the intensive phase and two drugs [H and R] in the continuation phase [13]. An eight month regimen consisted in H, R, E, Z and streptomycine (S) during the intensive phase and H, R and E in the continuation phase is used for the treatment of previously treated cases (relapses, failed and lost to follow-up cases). Multidrug-resistant patients are treated using the standard regimen for resistant tuberculosis that consists of second-line anti-tuberculosis drugs during 18 months or more [6]. The major contributing factor of the treatment effectiveness represents the right combination of the drugs according to the susceptibility results [7]. Without an appropriate treatment tuberculosis-related death occurs in average within 2 years. Due to high global epidemiological burden tuberculosis was located on the 5th place in the top of the causes of death [13]. Worldwide, there were estimated 580.000 new MDR-TB cases in 2015, but only 125.000 received an adequate regimen (DOTS-Plus) [18]. In the Republic of Moldova 25.5% of new cases and 70,6% of retreating cases were MDR-TB in 2015 [1]. All patients were treated with standard regimen for MDR-TB. The treatment succes rate in 2014 in the drug-susceptible HIV-negative cases constituted 79%, HIV-positive patients 47% and in multidrug-resistant tuberculosis (MDR-TB) cohort 53% [1]. For a better drug-resistance surveillance and precocious onset of the correct treatment rapid molecular test (GeneXpert MTB/Rif) is used by 15 Moldovan health care specialized institutions offering a 45% sensibility [5, 6]. However, the conventional methods: Lowenstein Jenson and BACTEC cultures remain the golden standard for *Mycobacterum tuberculosis* complex detection due to the simplicity

and low cost [6]. Low treatment adherence and high rate of lost to follow-up patients contributed to the development of a shorter conventional MDR-TB regimen lasting less than 12 months with low costs (<1.000$/patient) [18]. It showed promising results in selected MDR-TB patients and WHO updated its treatment guidelines in 2016 by including the recommendation to use the shorter MDR-TB regimen in patients with non-complicated tuberculosis (excluding extrapulmonary tuberculosis and pregnancy) [18]. Fluoroquinolones and pyrazinamide are key drugs in the new MDR-TB regimen, however, surveillance of the cross resistance in five high burden countries: Azerbaijan, Bangladesh, Belarus, Pakistan and South Africa established that resistance to rifampicine is frequently associated with resistance to pyrazinamide, so the effectiveness of the short regimen might be lower than predicted [13].

According to the WHO estimations MD remains a high risk zone showing an inadequate concern regarding tuberculosis social determinants that represent major barriers in achieving the health related Millennium Development Goals [10]. In the actual globalization process, MD is the least economically developed country of the Eastern European region. The major social determinants of tuberculosis and poor outcome are social and economic inequalities, high levels of internal/external migration, rapid urbanization and population growth in urban areas [4]. Such determinants result in the polarization of the public health interventions, poor housing, low environmental conditions, malnutrition, geographic and cultural barriers in access to the health care [11]. A profound interest is paid to the assessment of social determinants of low outcome among extremely poor populations: migrants, Gypsies, drug users, alcohol consumers, homeless people, as well as Inuit populations, North Indians, Arctic communities in North America [12, 14, 15]. There was identified a strong association of overcrowding, social isolation, poverty, unhealthy nutrition and persistence of tuberculosis in those marginalized populations.

There are several risk factors predictive of the disease outcome. First of all it is the infection with resistant and virulent mycobacteria [7]. It depends on the prevalence of sick people in the community. It is increased by the overcrowding, urban residence, poor indoor ventilation and pollution. It can be successfully managed at the administrative governmental level and by sanitation agencies. The second group includes the factors with risk for the disease relapse or recrudescence of the latent tuberculosis infection induced by such factors: phtysiogenic ages (infants less than 5 years, teenagers, elders aged 65 and more), the poverty-related conditions that contribute to malnutrition and co-morbid state, lack of BCG vaccination [16]. At this level more efficient are the activities of the epidemiologic agencies. The third group of risk factors influencing tuberculosis outcome are the determinants of the patient's immune status: HIV infection, immune suppressive drugs (>15mg/day of prednisolone for 1 month or more, immune modulators: TNF-α blockers or oral steroids, antineoplastic agents), diabetes, cancer, silicosis, chronic respiratory diseases, gastrointestinal diseases, underweight, phtysiogenic ages, harmful habits (tobacco smoking, alcohol abuse, illicit drug using) [9]. The most relevant actions for reducing the impact of those conditions must be performed by the primary health care sector and civil societies, through the active screening of high risk groups and their education [2, 3, 8]. The fourth group influencing the final outcome consists of the following risk factors: the accessibility of the sick people to the tuberculosis screening and health care, treatment compliance and patient's nursing [12]. In this group are included: lack of social protection and medical insurance, geographic and economic barriers, cultural behavior or stigma. Only the complementary relationship between primary health care, specialized sectors, social and community services can ensure the highest effectiveness of the disease control.

The aim of the study was to assess the determinants of loss to follow-up and tuberculosis patient's awareness. Objectives were: 1. Comparative assessment of tuberculosis indices in Chisinau and the Republic of Moldova during 2011-2015. 2. Assessment of the general, social, economic and epidemiological risk factors of lost to follow-up tuberculosis patients. 3. Evaluation of case-management, diagnosis, radiological aspects and microbiological characteristics of lost to follow-up patients.

Material and methods

It was performed a retrospective selective, descriptive study targeting social, demographic, economic and epidemiological peculiarities, case-management, diagnosis, radiological aspects and microbiological characteristics of 437 patients with pulmonary tuberculosis. The electronic system for monitoring and follow-up of tuberculosis cases (SIME TB) was used for the selection. Data were extracted from the statistic templates F089/1-e "Declaration about the patient's established diagnosis of new case/relapse of active tuberculosis and restart of the treatment and its outcomes". The inclusion criteria were: age > 18 years old, pulmonary tuberculosis, signed informed consent. The research schedule included demographic, social and epidemiological data: sex (male/female ratio), age, demographic characteristics (urban/rural), educational level, economical status (employed, unemployed, retired, disabled, student), health insurance status (presence/lack), history of migration and detention, high risks: close contact with an infectious source, co-morbidities (HIV-infection, diabetes, psychiatric diseases, immune suppressive treatment), health care seeking behavior, way of the patient's detection, patient's microscopic status. All selected patients were diagnosed and managed according to the National Clinical Protocol. Enrolled patients were distributed in two groups: the 1st group (1) was constituted of 165 patients successfully treated (cured - CG) in the period 01.01.2015-31.12.2015 and the 2nd group (2) was constituted of 272 patients lost to follow-up (LFUG) in the period of 01.01.2010-31.1201.2016.

Population awareness regarding various aspects of tuberculosis is important for the disease control at the na-

tional level. For the assessment of patient's knowledge was performed a pre-designed schedule containing open-ended and close-ended questions, reflecting various aspects of the tuberculosis. It included questions on how the patients heard about the disease, mode of transmission, symptoms, curability, type of drugs, duration of the regimen and the place of the treatment. Study technique was by exit interview. The sample size was constituted from 151 interviewed patients, that were 55.51% of the 2nd group. They were informed about the purpose of the study, were assured about their confidentiality and anonymity and the informed consent was taken. Statistic analysis was carried out using the quantitative and qualitative research methods. Statistical survey was performed using Microsoft Excel XP soft.

Results and discussion

According to the published data by the Moldovan National Centre for Management in Health during the period 2011-2015 it was registered an important decline of all notified cases (new case, retreated for relapse, loss to follow-up and failure) in MD by 27,8/100.000 and in Chisinau by 22,2/100.000 population (fig. 1).

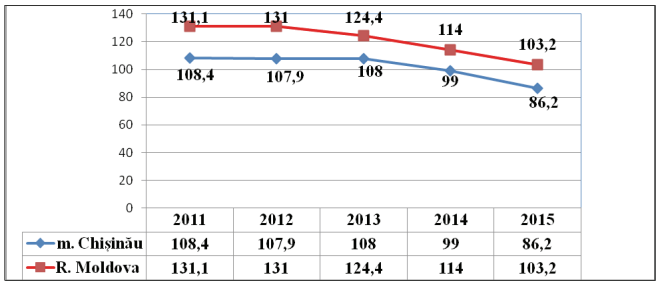

Fig. 1. Tuberculosis notification rate in MD and Chisinau/100.000 during 2011-2015.

Detection of the suspects for tuberculosis is based on the microbiological investigation. Ziehl-Neelsen method of acid fast bacilli staining and culture on the conventional media was performed in the assessment of every patient exposing clinical signs: productive cough for more than 3 weeks, weakness, decreased appetite, weight loss, fever and night sweats [6]. At least two sputum samples are collected in 8-24 hour interval, one sample being an early morning specimen [6]. However, the poor sensitivity of smear microscopy (less than 25%) and long delay in obtaining culture results (at least 120 days for providing a positive result) contribute to the late detection and increased proportion of severe and chronic forms of pulmonary tuberculosis [5]. The high rate of drug-resistant strains circulating in the population made compulsory the performing the nucleic acid amplification testing (GeneXpert MTB/Rif) to each suspected case [6]. By including the polymerase chain reaction in the standard algorithm was increased the sensibility of suspect's investigation [6]. As the consequence the rate of pulmonary clinical forms of tuberculosis is the highest among all diagnosed forms and maintains the similar value in the assessed period of time (fig. 2).

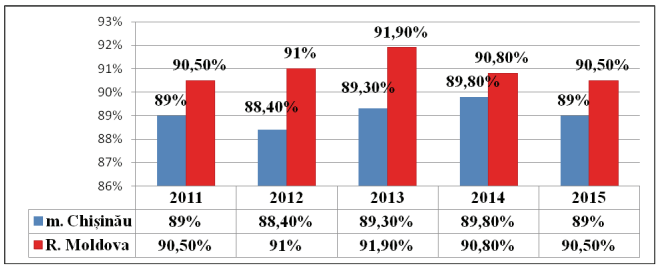

Fig. 2. Rate of pulmonary TB in MD and Chisinau during 2011-2015 (%).

Due to the improving of the treatment quality, the rate of died MDR-TB patients was continuously decreasing: 2011 – 51.7%, 2012 – 47.2%, 2013 – 46%, 2014 – 34.6%, 2015 – 23.2%. The treatment success rate increased (by 3.7%) from 2010 to 2014 in the microscopic positive patients: 2010 – 45%, 2011 – 56.7%, 2012 – 57.5% and culture positive cases 2013 – 70.3%, 2014 – 78.7% (fig. 3).

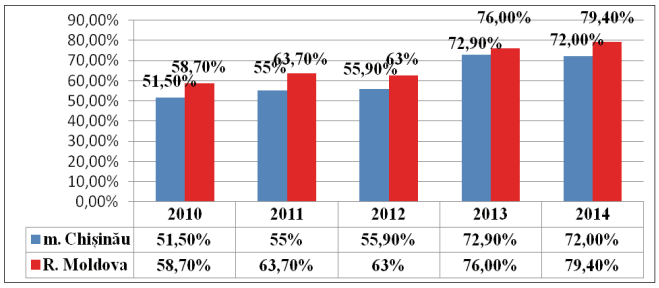

Fig. 3. Treatment success rate in MD and Chisinau during 2011-2015 (%).

The treatment failure rate showed a sharp decrease from 2010 to 2015 due to definition changes: 2010 – 26.9%, 2011 – 23.6% and 2012 – 18.2%. During this period of time all cases identified with MDR-TB and performing treatment for drug-susceptible TB were considered a therapeutic failure. Starting from 2013 patients with treatment failure were considered only patients with microbiological smear positive after 5 months of treatment. Actually the rate of treatment failure is very low: 2013 – 6% and 2014 – 2.8%. The rate of patients lost to follow-up decreased evidently: 2010 – 15.8%, 2011 – 16%, 2012 – 13.7%, 2013 – 9.3% and 2014 – 11.2%.

The proportion of patients lost to follow-up decreased during the period 2010-2015 by 16.4% in MD and by 4.7% in Chisinau due to implementation of the patient's centered health care (fig. 4).

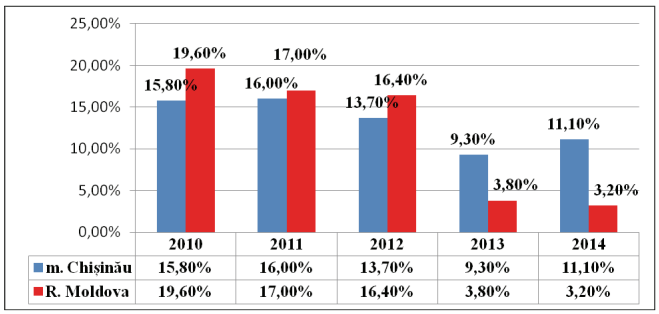

Fig. 4. Rate of lost to follow-up patients in MD and Chisinau during 2011-2015 (%).

Clinical study established a similar sex distribution in the cured (the 1st group) and lost to follow-up group (the 2nd group), with male/female ratio=4/1 in the 1st group and 3,86/1 in the 2nd group. Repartition of the patients into three age groups, identified that the largest was 35-54 year group, consisting from one half of every sample. Comparing the groups it was established that the rate of young, economically vulnerable and reproductive patients (aged 18-34) predominated in the 2nd group: 121 (44.48%) *vs.* 40 (24.24%) in the 1st group. Older patients (aged 55 and more) predominated in the 1st group. So, according to the biological characteristics of the selected patients it was established that men and women had the same probability to be cured or to default the treatment, but young cases have a higher risk for default than older patients. When distributing patients by demographic residence it was established a high predominance of rural residents in the lost to the follow-up group.

Table 1

Distribution of patients by demographic data

Indices	Sex Age Residence	CG (1) N= 165 (P %)	LFUG (2) N= 272(P %)	P value
Sex	Men	132 (80.00)	216 (79.41)	>0,05
	Women	33 (20.00)	56 (20.58)	>0,05
Age groups	18-34 years	40 (24.24)	121 (44.48)	**<0,001**
	35-54 years	91 (55.15)	137 (50.37)	>0,05
	> 55 years	34 (20.61)	14 (5.15)	**<0,001**
Residence	Urban	134 (81.21)	42 (15.44)	**<0,001**
	Rural	31 (18.78)	229 (84.51)	**<0,001**

When distributing the patients, according to the case-type it was established a higher rate of new cases in the 1st than in the 2nd group, without achieving statistical threshold. Relapse was in every fifth patient from both groups. Patients with a previous loss to follow-up statistically predominated in the 2nd group. The totality of the retreated patients predominated in the 2nd group – 116 (42.65%) comparing with 53 (32.12%) cases in the 1st group (p<0,05). Data are shown in the table 2.

Table 2

Distrbution in case-type according to the previous tuberculosis treatment history

Characteristics N= 165 (P %)		CG (1) N= 272(P %)	LFUG (2)	P value
New case (never treated)		112 (67.88)	156 (57.35)	>0,05
Retreatment	Relapse	35 (21.21)	49 (18.01)	>0,05
	After loss to follow-up	8 (4.85)	52 (19.12)	**<0,05**
	After treatment failure	10 (6.06)	15 (5.51)	>0,05

When distributing patients, according to the economic status, it was established that employed persons, contributing to the health budget by paying taxes, health insurance policy and social taxes predominated in the 1st group. The low rate of disabled patients in all groups demonstrated that most of them had no social protection and financial aid. Unemployed patients constituted the largest part of the 2nd group and one half of the 1st group. Patients in social vulnerable state, that included unemployed, disabled, retired and students predominated in 2nd group: 254 (93.38%) comparing with 124 (75.15%) cases, p<0,001. Patients without insurance were more numerous in the 2nd group (tab. 3).

Table 3

Economic status of patients with pulmonary tuberculosis

Economic indices	State	CG (1) N= 165 (P %)	LFUG (2) N= 272(P %)	P value
Stable	Employed	41 (24.85)	18 (6.62)	**<0,001**
	Disabled	9 (5.45)	16 (5.88)	>0,05
	Retired	12 (7.27)	4 (1.47)	>0,05
	Students	8 (4.85)	0	>0,05
Vulnerable	Unemployed	95 (57.57)	234 (86.03)	**<0,001**
	Lack of insurance	97 (57.57)	234 (86.03)	**<0,001**

When assessing the educational level it was established that one half of the 2nd group and one third of the 1st group graduated general school. The incomplete general studies had more frequently the patients from the 2nd group. Higher education was established in a limited number of cases. The totality of patients with low level of education which included no school attendance, primary and incomplete general school predominated in the 2nd group: 90 (33.09%) comparing with 45 (27.73%) cases in the 1st group. Exposed data are revealed in the table 4.

Table 4

Distribution of patients according to the last graduated level

Educational level	Educational status	CG (1) N= 165 (P %)	LFUG (2) N= 272 (P %)	P value
Illiteracy	No school attendance	1 (0.61)	9 (3.31)	>0,05
Primary level	Primary & general incomplete school	44 (26.67)	81 (29.79)	>0,05
Secondary level	Completed general school	57 (34.4)	147 (54.04)	**<0,001**
	Professional school	47 (28.48)	31 (11.39)	**<0,001**
Higher education	Superior studies	16 (9.69)	4 (1.47)	>0,05

When distributing patients in high risk groups, it was determined that poor living conditions and extreme poverty (homeless) predominated in the 2nd group. History of migration during the last year and history of imprisonment statistically predominated in the 2nd group. The lowest rate of the family TB clusters affiliated to each investigated patient was linked with the low quality of epidemiological cross-examination. Patients with associated diseases were every fourth from each group. Among associated diseases, HIV infection was

established in a similar proportion in both groups. Chronic alcohol abusers were 26 (9.59%), drug users – 5 (1.84%) and psychiatric disorders had 4 (1.47%) patients in the 2nd group. No such cases were established in the 1st group. Data are shown in the table 5.

Table 5

Distribution of patients in high risk groups

Risk groups	CG (1) N= 165 (P %)	LFUG (2) N= 272(P %)	P value
Poor living conditions	42 (25.45)	127 (46.69)	<0,001
Homelessness	12 (7.27)	36 (13.23)	>0,05
Migration	20 (12.12)	70 (25.73)	<0,001
History of detention	3 (1.81)	56 (20.58)	<0,001
Closed contact	4 (2.42)	19 (6.98)	>0,05
Associated diseases	42 (25.45)	72 (26.47)	>0,05
HIV infection	15 (9.09)	25 (9.19)	>0,05

Studying case-management, it was identified that the staff of the primary health care detected one half of the 1st group and every fourth patient in the 2nd group as symptomatic cases. The rate of patients detected by the high risk groups screening was low and demonstrated poor control of the vulnerable populations. Pulmonologists diagnosed as symptomatic and by high risk group screening a low rate of patients from both groups. Direct addressing to the specialized hospitals was used more frequently by the patients from the 2nd group due to the lack of health insurance and avoidance of primary health care staff. Other ways of detection were rarely used and included detection of patients hospitalized in the clinical hospital (tab. 6).

Table 6

Case-management characteristics of selected patients

Health level	Detection ways	CG (1) N= 165 (P %)	LFUG (2) N= 272 (P %)	P value
PHC	Detected by GPs as symptomatic cases	69 (41.82)	73 (26.83)	**<0,01**
	Detected by GPs through the screening of HRG	30 (18.18)	35 (12.87)	>0,05
Ambulatory specialised level	Detected by SP as symptomatic cases	22 (13.33)	31 (11.39)	>0,05
	Detected by SP through the screening of HRG	11 (6.67)	23 (8.45)	>0,05
Hospital level	Direct addressing to the specialized hospital	30 (18.18)	107 (39.34)	**<0,001**
Other	Other ways	3 (1.82)	3 (1.11)	>0,05

Note: PHC-primary health care, GPs-general practitioners, SP-specialist pneumophtysiologist, HRG-high risk groups.

When identifying the clinical radiological forms of pulmonary tuberculosis it was established that infiltrative tuberculosis was diagnosed in the most of the patients of both samples, however, it predominated in the 1st group. Severe, chronic forms, which included disseminated, generalized and fibro-cavernous tuberculosis predominated in the 2nd group – 41 (15.07%) comparing with 11 (6.67%) patients in the 1st group, p<0,01. Distributing patients, according to the number of the affected lungs, it was established that one lung was involved in two thirds of the 2nd and one half of the 1st group and both lungs were affected in two thirds of the 2nd group and one half of the 1st group. Destructive forms of pulmonary tuberculosis were identified in a similar proportion in both groups. Extrapulmonary localizations were identified only in the 2nd group (tab. 7).

Table 7

Distribution of patients according to the radiological characteristics

Parameters	Detection ways	CG (1) N= 165 (P %)	LFUG (2) N= 272 (P %)	P value
Forms of TB	PIT	154 (93.33)	223 (81.98)	>0,05
	PDT	9 (5.45)	21 (7.72)	>0,05
	Generalized TB	0	1 (0.36)	>0,05
	FCVTB	2 (1.21)	19 (6.98)	>0,05
Localization and features	1 lung	90 (54.54)	61 (22.42)	**<0,001**
	Both lungs	75 (45.54)	211 (77.57)	**<0,001**
	Lung destruction	79 (47.88)	150 (55.15)	>0,05
Extrapulmonary	Pleurisy	0	3 (1.11)	>0,05
	Other forms	0	5 (1.84)	>0,05

Note: PIT – pulmonary infiltrative tuberculosis, PDT- pulmonary disseminated tuberculosis, FCVTB – fibro-cavernous tuberculosis.

When assessing the laboratory features it was identified that one half of both samples were microscopic positive for acid-fast-bacilli. Culture positive have been more numerous patients from the 2nd group. Multidrug-resistance was established in one third of the 2nd group and every tenth patient from the 1st group. Drug sensitivity testing identified a low proportion of patients with mono- and poly-resistant tuberculosis in both groups (tab. 8).

Table 8

Distribution of patients according to the microbiological features

Characteristics N= 165 (P %)		CG (1) N= 272 (P %)	LFUG (2)	P value
Microbiological	Microscopic positive	86 (52.12)	149 (54.78)	>0,05
	Culture positive	73 (44.24)	156 (57.35)	**<0,01**
	MDR-TB	22 (13.33)	79 (29.04)	**<0,001**
	Mono-resistance	6 (3.64)	3 (1.11)	>0,05
	Poly-resistance	4 (2.42)	6 (2.26)	>0,05
GeneXpert MTB/Rif	Sensible	98 (59.39)	N/A	-
	Resistant	15 (9.09)	N/A	-
	GeneXpert MTB/Rif positive	117 (70.91)	N/A	-

An important research outcome represents the calculation of the likelihood ratio, relative risk (RR), odds ratio

(OR) and the attributable risk (AR). They were used for identifying the high risk groups targeted for the priority interventions for reducing the probability of loss to follow-up. All risk factors exposed statistical difference between groups. The hierarchy of risk groups according to the probability (likelihood ratio) to default the treatment had patients from rural areas, living in poor conditions, with the life history of detention, unemployed and those who addressed to the specialized hospitals avoiding the primary health care. Major factors assessed through relative risk and odds ratio were: life history of detention, rural residence, poverty, unemployment and direct addressing to the hospital. According to the attributable risk hierarchy of risk groups was: life history of detention, rural residence, recent history of migration, patients with MDR-TB, direct addressing to the hospital, poverty, previously treated patients and unemployment. Data are shown in the table 8.

Table 8

Risk factors of tuberculosis patients for loss to follow-up

Factors P		Statistical indices				AR
		LR	RR	OR	%	
Demographic	Rural residence	0	194,966	6,38	23,56	80.98
Treatment	Previously treated	0,02	4,85	1,33	1,57	43.96
Social economical features	Unemployment	0	43,77	2,24	5,53	33.08
	Poverty	0	171,029	5,3	18,31	45.49
	Migration	0,0006	12,358	1,88	2,51	52.89
	History of detention	0	101,51	3,29	46,07	91.20
Case-related	Direct addressing to the hospital	0	76,49	2,57	8,16	53.78
	MDR-TB	0,00016	15,141	1,93	2,66	54.09

Note: P value according to the Pearson's test, LR-likelihood ratio, RR-relative risk, OR-odds ratio; AR-attributable risk.

Population awareness regarding various aspects of tuberculosis is important for the disease control at the national level. For the assessment of patient's knowledge was performed a pre-designed schedule containing open-ended and close-ended questions, reflecting various aspects of the tuberculosis. It included questions on how the patients heard about the disease, mode of transmission, symptoms, curability, type of drugs, duration of the regimen and the place of the treatment. Study technique was by exit interview. The sample size was constituted from 151 interviewed patients. They were informed about the purpose of the study, were assured about their confidentiality and anonymity and the informed consent was taken.

When the patients were asked about how they received information related to tuberculosis it was revealed that most of all [121 (80%)] were informed by the health personnel. About 30 (19.87%) had heard from an informal contact: 17 (11%) mass media (radio, television, posters), 8 (5%) family and 5 (4%) from friends (figure 5). When they were asked if they were satisfied by the conversation with health personnel about their disease 141 (51,845) answered "yes".

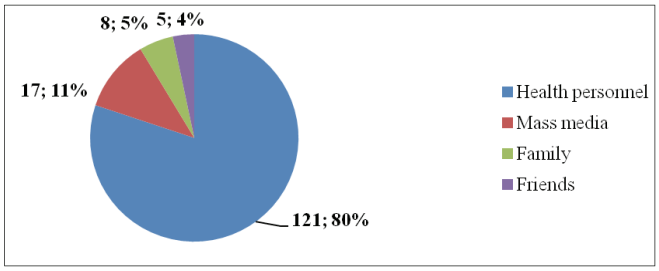

Fig. 5. Distribution of the patients according to the source of knowledge (abs., %).

When the patients were asked about the cause of tuberculosis, 142 (94.04%) answered "infection". Regarding the mode of the spread of infection most of them, 132 (87.42%) patients, answered, correctly choosing multiple choice: cough, spit, speaking and talking face-to-face with a sick person (fig. 6).

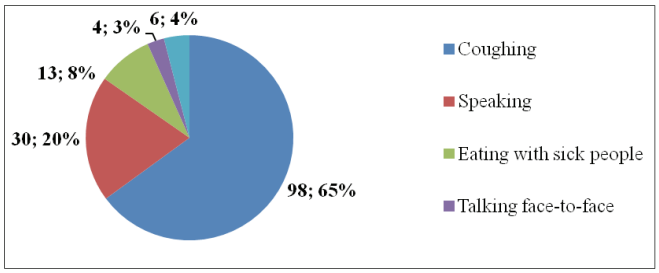

Fig. 6. Distrbution of patients according to the knowledge about the mode of the spread of infection (abs.,%).

The patients were asked about which organ can be affected by tuberculosis. Most of them [140 (92.72%)] answered "lung" and only a low proportion "lungs and other organs" (fig. 7).

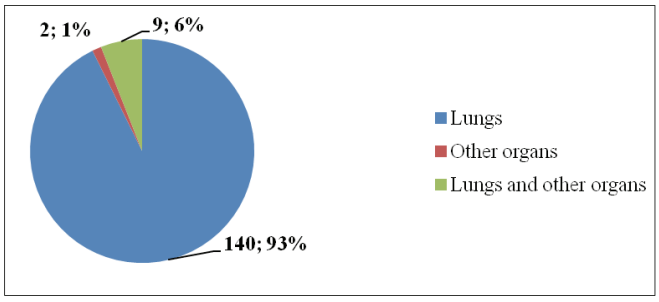

Fig. 7. Distrbution of the patients according to knowledge about the affected by tuberculosis organs (abs.,%).

When they were asked if the disease is curable, 140 (92.71%) patients answered "yes", but only 52 (34.44%) recognized that were previously treated for tuberculosis. For the establishing the patient's therapeutic compliance they were asked if there is a risk to develop resistance if the treatment

is taken irregularly or interrupted. Only 110 (72.85%) patients answered "yes". They were asked if the smear microscopy is negative, it is allowed to interrupt the treatment and 16 (10.59%) patients answered correctly "yes". At the question if they can take two dosages if the previous dosage was lost, 143 (94.71%) patients answered correctly "no". When asked how many months it is necessary to be treated to be cured, 77 (50.99%) said "more than 6 months", 55 (36.42%) – "more than one year", 8 (5.29%) – "two-three months" and 11 (7.28%) did not answer. They were asked where they want to be treated and 111 (73.51%) answered "in the hospital" and only 40 (26.49%) in outpatient settings.

Conclusions

The standard treatment of a new drug-susceptible case, according to WHO guidelines, lasts 6 months and of drug-resistant case – 18-24 months. It must achieve a treatment success rate of at least 85%. Long duration, the high rate of drug adverse reactions and low patient's awareness about treatment compliance contribute to loss to follow-up of at least every tenth patient in MD.

The tuberculosis notification rate in MD decreased evidently in the last 5 years due to the low rate of sreening performed in the high risk groups. The treatment success rate in MD increased evidently due to the excluding of the MDR-TB group from the general cohort. The rate of lost to follow-up patients remains high in Chisinau, despite an evident decrease in the entire country.

No differences were identified distributing patients, according to the sex. Younger patients were more frequent among those who drop up the treatment, but older patients were more frequently cured. Rural residence was associated with loss to follow-up, probably due to low accessibility to specialized health care settings.

Patients previously treated, constituted one half of the lost to the follow-up group. Treated after a previous loss to follow-up was every fifth patient.

Most of the patients from the lost to follow-up group were economically vulnerable. Lack of health insurance and social vulnerability constituted the major barriers for health care seeking. Low level of education had one third of both samples.

Patients from high risk groups designed by the national policy (HIV-infected, close contacts) represented only every tenth case. The highest proportion constituted TB-HIV co-infected patients. However, high risks such as poverty and comorbid status were established in every second patient from the group of lost to follow-up.

Cured patients were detected by general practitioner more frequently and patients treated after loss to follow-up came to the specialized hospitals avoiding primary health care. Severe forms, involving both lungs complicated with extrapulmonary localizations have been more frequent in the group of the lost to follow-up patients.

The proportion of bacteriological positive and drug-resistant patients was the highest in the lost to follow-up group, demonstrating the epidemiological danger that they expose on the healthy population.

The hierarchy of risk groups according to the highest proportion was established: ex-detainees, rural residents, migrants, infected with drug-resistant strains, addressed to the hospital, poor cases, unemployed and previously treated.

The awareness of the patients was good. Most of them were informed by the health personnel and were satisfied by the received knowledge. The proportion of those who were informed through the mass media was high. Most of the patients knew that the disease is contagious, is spread through the air and affects the lungs.

Despite the received information, every third patient lied that had never been treated before, all of them being patients treated after loss to follow-up. Most of the patients knew that the disease is curable with a complete treatment; however, every tenth considered that two-three months are sufficient. Considering their economic vulnerability two thirds wanted to be treated in the hospital.

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Methodology of computed tomography of maxillofacial and craniocerebral regions by means of vertical fixation of the examined objects

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Abstract

Background: The research aims at identifying new methodological approaches to the study of morphological patterns of prenatal development of the human upper jaw.
Material and methods: A working model has been developed and a device has been proposed, reasonable to be used for fixation of the examined object in a vertical position during computed tomography of maxillofacial and craniocerebral regions. For proper operation of the device there was introduced a method of vertical fixation of the examined objects during computed tomography of maxillofacial and craniocerebral regions.
Results: In the basis of the useful model lies the task to develop a method of vertical fixation of objects under study during the computed tomography of maxillofacial and craniocerebral regions by holding the examined object of up to 540 mm in size; the object is fixed to the planetable using the right and left retainers that are fixed in vertical openings; the height is regulated with the help of the rack, connecting the planetable with the tripod; swivel mounting is led to the facial part of the examined object and the chin is fixed on the table; then the vertical and horizontal position of the chin is regulated by means of sliding vertical and horizontal mounting; the fixed examined object is then moved to the CT scanner with the help of mobile tripod supports.
Conclusions: The proposed method is effective for vertical fixation of examined objects during the computed tomography of maxillofacial and craniocerebral regions in the desired position, that contributes to getting qualitative indicators of the examination and can be used during the spot-film radiography in direct and lateral projections in stable and desired position of the head and at the correct distance without imposing additional densities (shades) to provide accurate diagnostic results.

Key words: human fetus, maxillofacial and craniocerebral regions, vertical fixation, CT examination, upper jaw.

Introduction

Currently human anatomy deals with the shape and structure of organs, systems and human body in general as a product of heredity, which changes depending on certain conditions of biological and social environment and activities performed by the body, both in time (phylo- and ontogenesis) and in space (different geographical areas), synthesizes data of allied and related disciplines – histology, cytology, embryology, biochemistry, comparative anatomy, physiology, biophysics, etc. [1, 2, 12, 18]. The study of developmental peculiarities of anatomical structure of the teeth-jaw system in prenatal period of human ontogenesis is a topical direction in morphological investigations, which contributes to the solution of the important medical and social problem – improvement of preventive methods, early diagnostics and effective correction of congenital defects and treatment of acquired diseases of the upper jaw in man [10, 14, 16, 17]. Under the influence of a number of external factors certain malformations are observed in children even if they do not have obvious dental disorders, those are variations in terms of the teeth eruption and second dentition, the duration of their mineralization and roots formation compared to the terms and duration of these processes, presented by the researchers of the second half of the last century and therefore they need to be reviewed and refined [4, 5, 6, 7, 8, 9]. Data present in classical literature on embryology and meaningful publications are based on general biological foundation. Being steadfast, they do not disclose in detail a number of specific issues that are being discussed and the topic continues to attract researchers' attention in both general-theoretical and applied aspects [12, 15, 19]. Search for new methodological approaches to the study of morphological patterns of prenatal development of the upper jaw in man constitutes the objective of the study.

Material and methods

We have developed a working model and proposed the invention "Device for vertical fixation of examined objects during the computed tomography of maxillofacial and craniocerebral regions" for which priority of applications for invention was received [11], it refers to medicine, namely to anatomy, topographical anatomy and operative surgery, dentistry, pathological anatomy, morphology, forensic medicine, radiology, and can be used during the computed tomography of maxillofacial and craniocerebral regions to fix the examined object in the vertical position. It is for proper operation of the device [11] that we have developed a method of vertical fixation of the examined objects during the computed tomography of maxillofacial and craniocerebral regions [13].

The method was developed in the framework of the planned complex research work "Morphogenesis patterns and structural and functional properties of tissues and organs in human ontogenesis" of the department of histology, cytology and embryology; department of pathological anatomy of Higher State Educational Institution of Ukraine "Bukovinian State Medical University" (state registration № 0116U002938).

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Results

It is known that the possibility of computed tomography (CT) is characterized by the hardware-controlled reconstruction of one-time received images in different anatomical planes (projection) as well as by the three-dimensional reconstruction and provides the opportunity not only to assess the size, but also to study their structural features in detail and even some physiological characteristics based on the X-ray density [5, 6, 11].

The examined objects are usually placed horizontally on standard rail tables during the computed tomography. However, such examination of the objects is not ergonomic. We proposed to use dental scanners for this purpose, but they do not provide the placement of the examined object in the desired position with vertical fixation.

An important condition for ensuring dental CT is the motionless position of the examined object because movements during the study result in the occurrence of targeting artifacts: dark colored stripes from the formations with low air absorption coefficient and white stripes from the structures with high contrast index (bone, metal clips), which also reduce the diagnostic capacities, because receiving the image of the examined object by dental CT is achieved using a circular movement of the X-ray tube (240°).

Consequently, the urgent task is a versatile and convenient in operation fixation of the examined object in a vertical position with the regulation of distances in a stable and desired position, without impeding the scanning of examined areas and without imposing additional densities (shade) that provide accurate results.

The useful model analogue is a method of fixation [3] by means of the apparatus "RAYSCAN Symphony M", producing company DENNIME Bundang Technopark 3-408, KOREA, in which the face is fixed motionless, namely the jaw and the nose, in a standard vertical retainer of the dental tomograph of seated type. The prototype of the utility model is a method of fixing the corpses of fetuses and newborns in a normal anatomic position for morphological studies [20], in which the corpses of fetuses and newborns are fixed in a rectangular wooden frame, 30×50 cm in size, with a cross bar in the middle using 12 loops in-built into the inlets made in the upper and lower walls of the frame at a 7.5 cm distance, in the side walls of the frame at a distance of 12.5 cm from its outer edge, in the cross bar of the frame they are made at a distance of 5.5 cm from its inner edge, and 8 clamps.

In the basis of the useful model [13] lies the task to develop a method of vertical fixation of objects under study during the computed tomography of maxillofacial and craniocerebral regions by holding the examined object of up to 540 mm in size; the object is fixed to the planetable using the right and left retainers that are fixed in vertical openings; the height is regulated with the help of a rack, connecting the planetable with the tripod, for this reason it is fixed with the coupling inside the tripod tube; swivel mounting is led to the facial part of the examined object and the chin is fixed on the table; then the position of the chin in the vertical direction is regulated by means of sliding vertical mounting that is fixed by a plate of vertical mounting, and in the horizontal direction by means of sliding horizontal mounting that is fixed by a plate of horizontal mounting; the fixed examined object is then moved to the CT scanner with the help of wheels attached to the tripod supports.

Theoretical background of the utility model development. Computer methods of diagnostics have recently become extensively developed, in particular computed tomography, which provides highly accurate images of osseous tissues.

CT solves the problem of accuracy, high reliability and objectivity and reduces the time of the examination.

The use of CT reduces signal distortion and radiation exposure, providing high contrast and sharpness of images, convenience and reliability while storing the information.

The advantage is that CT allows performing the examination of animal carcasses, human fetuses and newborns without autopsy. But such objects are specific due to their size and condition. Thus, the most productive for their study is the use of mobile dental scanners, for which the necessary prerequisite is a vertical fixation of the examined object.

Currently there are no specialized convenient ways of fixing such objects, the main task of which is to maintain normal anatomical position of the corpse. To solve this problem fixation should be carried out by adjusting the distances in both vertical and horizontal directions. One of the essential tasks is also to exclude the imposition of additional density (shade) to obtain clear images and accurate research results.

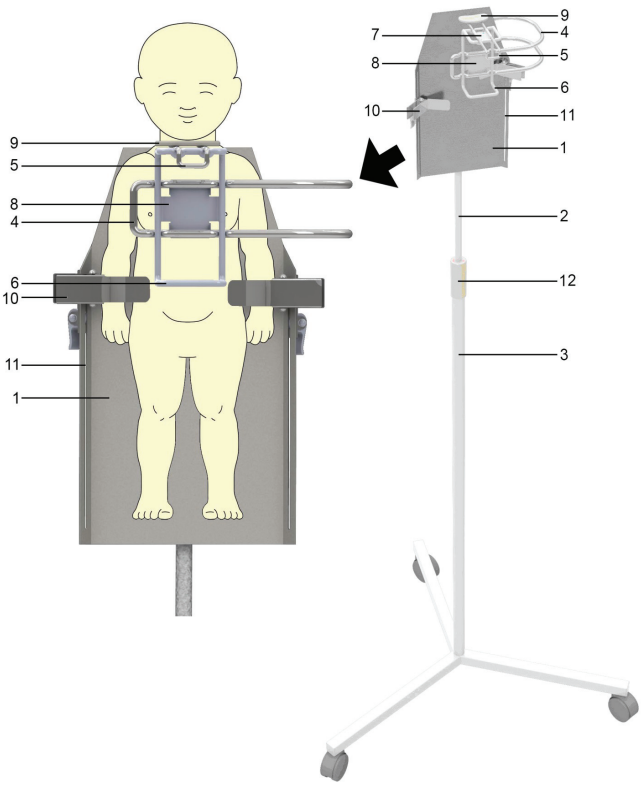

Fig. 1. Demonstration of the method of vertical fixation of the examined object for performing computed tomography of maxillofacial and craniocerebral regions (scheme).

In order to achieve the above mentioned objectives the given utility model [13] represents a versatile and convenient in operation method of fixation of the small-sized examined objects in a vertical position with the regulation of distances of vertical and horizontal positions by means of the device [11] that does not impede the laser scanning and does not cause the imposition of additional densities (shade) that provides accurate results.

Figure 1 demonstrates the method of vertical fixation of the examined object for performing computed tomography of maxillofacial and craniocerebral regions. Figure 2 shows the enlarged side view of the method.

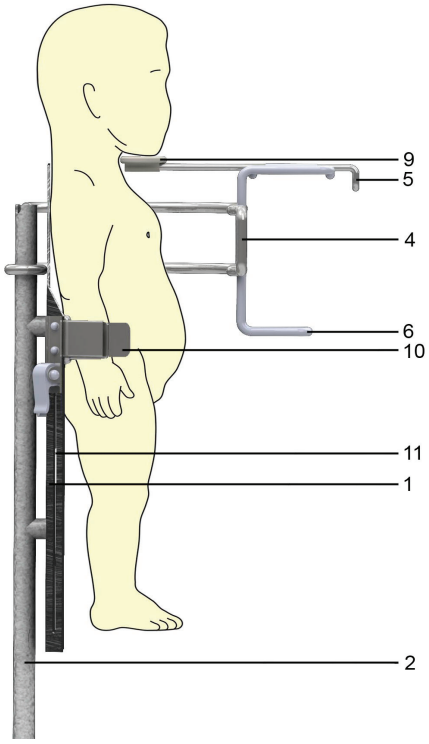

Fig. 2. Enlarged side view of the method of vertical fixation of the examined object for performing computed tomography of maxillofacial and craniocerebral regions (scheme).

The utility model [13] is implemented in the following way. The examined object of up to 540 mm in size is fixed to the planetable 1 using the right and left retainers 10, that are fixed in vertical openings 11; the height is regulated with the help of the rack 2, connecting the planetable 1 with the tripod 3, for this reason it is placed inside the tripod tube and fixed with coupling 12. Swivel mounting 4 is led to the facial part of the examined object and the chin is fixed on the table 9 located on it. Then the position of the chin in the vertical direction (on 40 mm) is regulated by means of sliding vertical mounting 6, that is fixed by a plate of vertical mounting 8, and in the horizontal direction (on 45 mm) by means of sliding horizontal mounting 5, that is fixed by a plate of horizontal mounting 7. The fixed examined object is then moved to the CT scanner with the help of wheels attached to the tripod 3 supports.

Discussion

The disadvantage of the analogue method [3] is that there is no possibility to fix small examined objects (up to 540 mm) (fetuses); the method does not provide the fixation of corpses of such objects in the normal anatomical position.

The disadvantages of the prototype method are the following [20]: considerable loss of time for the fixation of the examined object with the loops, impossibility of regulating the distance in both vertical and horizontal directions to provide the desired position by using non-removable rectangular wooden frame; vertical fixation requires additional equipment, impossibility of imager head passing and imposition of additional density (shade).

Common feature of the useful model [13] and the prototype [20] is a vertical fixation of the examined objects (corpses) of small size with the help of in-built parts.

Distinctive features of the useful model [13] and the prototype [20] are: the examined object of up to 540 mm in size is fixed to the planetable using the right and left retainers that are fixed in vertical openings; the height is regulated with the help of the rack, connecting the planetable with the tripod, for this reason it is placed inside the tripod tube and fixed with coupling; swivel mounting is led to the facial part of the examined object and the chin is fixed on the table; then the position of the chin in the vertical direction is regulated by means of sliding vertical mounting that is fixed by a plate of vertical mounting, and in the horizontal direction by means of sliding horizontal mounting that is fixed by a plate of horizontal mounting; the fixed examined object is then moved to the CT scanner with the help of wheels attached to the tripod supports.

Example of the utility model use. The offered method of the vertical fixation was used during CT procedure in 25 macropreparations of human fetuses by means of Plameca apparatus with software I-CAT with digital recording and data analysis.

It was found that the offered method of vertical fixation of the examined objects during the computed tomography of maxillofacial and craniocerebral regions is effective at the expense of regulating the distance of vertical and horizontal position by means of the device [11], that does not impede laser scanning and does not cause the imposition of additional densities (shade) during X-ray irradiation.

All studies were conducted in compliance with the substantive provisions of GCP (1996), European Convention on Human Rights and Biomedicine (of 04.04.1997), Helsinki Declaration of the World Medical Association on ethical principles of scientific medical research involving human (1964-2013), Orders of Ministry of Health of Ukraine № 690 dated 23.09.2009, № 616 dated 03.08.2012.

Conclusions

The proposed method is effective for vertical fixation of the examined objects during the computed tomography of maxillofacial and craniocerebral regions in the desired posi-

tion, that contributes to getting qualitative indicators of the examination and can be used during the spot-film radiography in direct and lateral projections in stable and desired position of the head and at the correct distance without imposing additional densities (shades) to provide accurate diagnostic results.

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Compliance with ethical standards.

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Surgical treatment of patients with hemorrhoids by using traditional and minimally invasive methods

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Abstract

Background: Hemorrhoids are a common pathology of the ano-rectal region and their treatment remains relevant. New minimally invasive methods of surgical treatment of hemorrhoids have been developed recently. Transanal Doppler-Guided Hemorrhoidal Artery Ligation (DG-HAL) of internal hemorrhoids is an up-to-date minimally invasive surgical method of hemorrhoid treatment. In the Republic of Moldova, many patients seek medical help only in advanced stages with large prolapse. It is not always possible to resolve the problem with minimally invasive methods. In medical literature there is little elucidation of the simultaneous combination of the DG-HAL method with the excision of external hemorrhoidal nodes. In the Republic of Moldova this study is being carried out for the first time. The authors present the results of combined surgical treatment of patients with hemorrhoids. The combined method of surgical treatment of hemorrhoidal disease has been implemented in our country and the efficacy of the method for individual approach has been demonstrated.

Material and methods: The results of the surgical treatment of 15 patients with the diagnosis of chronic hemorrhoids III-IV grade were evaluated. Patients were treated with the combined surgical method (DG-HAL with excision of hypertrophied external hemorrhoids and / or skin tags).

Results: Postoperative pain after "visual analogue scale" ranged from 3 to 6. Postoperative hospitalization constituted from 1 to 6 days. The duration of the surgery during adoption of approach was 30-60 minutes, but in the years 2016-2017 it constitutes 25-40 minutes. Severe complications have not been detected.

Conclusions: The individual approach by combined surgical treatment of patients with hemorrhoidal disease improves treatment outcomes.

Key words: proctology, hemorrhoids, surgical treatment, artery ligation, desarterization.

Introduction

Hemorrhoidal disease is one of the most common human diseases, and occupies the first place in the structure of coloproctological diseases. Taking in consideration the delicacy of the problem in most cases the patient seeks a doctor in advanced stages. According to World Health Organization, more than 70% of the world population is predisposed to hemorrhoidal disease. According to epidemiological studies, the prevalence of hemorrhoids in the United States is estimated at 4.4% or 8.5 million patients. In the structure of the ano-rectal diseases, hemorrhoidal disease is approximately 40%. One of three of these patients needs surgical treatment [1, 2, 3, 8, 9, 12].

The problem of treating hemorrhoidal disease remains relevant. In connection with scientific and technological progress, which is reflected in medicine, in recent years, new minimally invasive methods of surgical treatment of hemorrhoidal disease have been developed. Transanal Doppler-Guided Hemorrhoid Artery Ligation (DG-HAL) of Internal Hemorrhoids is a modern, minimally invasive method for the treatment of hemorrhoidal disease. However, in advanced stages of hemorrhoids, it is not always possible to solve the problem of pronounced prolapse of hemorrhoidal nodes with the help of minimally invasive surgical methods.

According to published medical literature regarding the postoperative period, in some patients who underwent only DG-HAL or Hemorrhoidal Artery Ligation with Recto-anal Repair (HAL-RAR) the problem of prolapse of hemorrhoids and the presence of skin tags remained unsolved. Patients complained of residual prolapse and the presence of "skin tags", causing discomfort. In order to avoid a two-stage surgical correction of hemorrhoidal disease, we consider it expedient to have an individual approach to surgical intervention.

In this regard, the authors share the results of their experience of combined surgical treatment of patients with hemorrhoidal disease.

Material and methods

All 15 surgeries were performed with the second-generation A.M.I. HAL-Doppler II device (fig. 1). Proctoscope with the doppler ultrasound transducer (RAR Flexi Probe) sends signals to the A.M.I. HAL-Doppler II device, where the pulsating waves transform into the sound signal that is displayed on the monitor through a graphical representation (curve) corresponding to the pulse of the branches of the upper hemorrhoidal artery. During surgery, its branches are detected, where proximal to the dentate line the transanal ligation procedure of the arteries is performed (DG-HAL). Mucopexy (lifting) of the mucosa and prolapsed hemorrhoidal nodes have not been performed in this group of patients. All the surgeries were performed under spinal anesthesia, which allowed relaxation of the anal sphincter. For the ligation of hemorrhoidal arteries, the surgical sutures 2-0, with 5/8 needle from the device manufacturer (Austria) was used. During the period from 2014 to 2017, 15 combined surgeries were performed at the Department of Surgery No. 5 in the treatment of patients with internal hem-

orrhoids grade III-IV combined with external hemorrhoids and/or skin tags. The first stage of the operation consisted in carrying out transanal doppler-guided artery ligation of the branches of the upper hemorrhoidal artery (DG-HAL). The second stage of the operation consisted in the excision of external hemorrhoids, depending on the individual characteristics of the patient.

Fig. 1. A.M.I. HAL-Doppler II device.

Results

In the postoperative period, all patients had a significant reduction or lack of symptoms of hemorrhoidal disease (bleeding from the rectum, itching, discomfort, etc.). None of the patients had prolapse of hemorrhoids. During surgical interventions, significantly less bleeding was observed during excision of external hemorrhoids and skin tags, because this was preceded by transanal ligation of the branches of the upper hemorrhoidal artery under the control of ultrasound dopplerometry. In 1 year the outcomes were analyzed in 10 patients out of 15, in 6 months – in 3patients, and in 3 months – in 2patients. Postoperative pain after "visual analogue scale" ranged from 3 to 6.The average length of stay in the hospital after the surgery in patients who underwent combined treatment was 1-6 days. The duration of the surgery (min) during adoption of approach was 30-60 minutes, and in the years 2016-2017 it constitutes 25-40 minutes. In this category of patients there were no complications in the late postoperative period registered.

Discussions

There is a big amount of literature data and scientific articles describing the results of various mini-invasive and traditional methods of surgical treatment of hemorrhoidal disease. Recently, experience and analysis of the results of treatment of patients with the help of transanal dopplerometry are being accumulated [7, 8, 9, 10, 11, 12, 13, 14]. Lately, there are publications with comparative results of HAL-RAR with other methods [15, 16, 17, 18, 19, 20, 21]. However, there is practically no data on the combination of mini-invasive methods with the traditional methods of surgery during one surgical intervention [22].

A search was made for the results of combined surgical treatment of hemorrhoids in the scientific medical bases of PubMed and Web of Science. We were especially interested in combining the HAL-RAR method with traditional ones, because in the advanced stages it was not always possible to solve the problem of pronounced prolapse using only the minimally invasive method. The results of the search for the first 30 articles on key words (hemorrhoids, HAL RAR, hemorrhoidal artery ligation, recto anal repair, DG-HAL, THD, dearterialization, doppler, simultaneous, combined, surgical, treatment) and their combinations were analyzed,

The combined approach in the surgical treatment of this category of patients has good results in treating the symptoms of hemorrhoidal disease (rectal bleeding, prolapse of hemorrhoids, itching, discomfort, etc.). In our opinion, the risks of serious postoperative complications, more typical for classical traumatic operations (stricture, incontinence, dysuric disorders, bleeding, purulent-inflammatory complications, etc.) are reduced. Also, the duration of surgical excision of external hemorrhoids was shortened. In our opinion, this is due to a decrease in blood flow to the hemorrhoids after DG-HAL. Taking into account the effect on the vascular component, the use of this method is considered pathogenetically justified. Undoubtedly, to achieve good results, an individual, differentiated approach to conservative and surgical treatment of hemorrhoidal disease is fundamental. In case the patient has an internal symptomatic hemorrhoids II-III degree (according to Goligher) DG-HAL or HAL-RAR are carried out. If the patients who suffer from internal hemorrhoids of III-IV degree to perform HAL-RAR, they may possibly need additional surgical correction of massive prolapse.In case the patient is diagnosed with combined hemorrhoids with pronounced prolapse (internal hemorrhoids of III-IV degree in combination with external hemorrhoids, and the presence or absence of "skin tags"), we consider it optimal to perform combined surgical intervention (DG-HAL with excision of external hemorrhoidal nodes +/- "skin tags").

The pain syndrome in all 15 patients was less pronounced compared with classical methods, but higher than when performing exclusively DG-HAL or HAL-RAR without tissue excision. Postoperative pain syndrome after using the combined method varied depending on the volume of excision of external hemorrhoidal nodes and skin tags, and was individually assessed according to the VAS and effectively controlled.

As a result of combining traditional methods of excision of external hemorrhoidal nodes and skin tags with HAL, the following advantages were obtained: 1. Minimal intraoperative hemorrhage, that has contributed to reducing the time required to perform that excision, 2. For all patients, the problem of anal prolapse and hemorrhoidal disease has been solved.

Conclusions

1. Combined surgical treatment of hemorrhoidal disease is quite effective.

2. Method is pathogenetically grounded, more radical in

comparison with modern minimally invasive methods and less traumatic than classical surgical methods.

3. We believe that this method of combined hemorrhoidal treatment can be recommended for this category of patients.

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Clinical presentation, risk factors and outcomes of tuberculosis in military recruits

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Abstract

Background: Tuberculosis represents the major threat for the health protection in the military forces**.** The aim of this retrospective and descriptive study was the evaluation of risk factors, clinical presentation and treatment outcomes of tuberculosis in military recruits.
Material and methods: 51 military recruits with tuberculosis diagnosed during 01.01.2010-31.12.2015 in Chisinau military quarters and managed in the Hospital of Pneumophtysiology were assessed.
Results: Most of military recruits aged 18-22, were residents of the rural localities, graduated incomplete general school or lyceum and were economically vulnerable. One half of the group consisted of active smokers and every tenth patient abused alcohol. Every fourth patient had tuberculosis in childhood and every tenth had family contact with a tuberculosis-affected person. Disease's insidious onset was established in one half of the group and the acute onset in every fourth patient. Every tenth patient was diagnosed with tuberculosis within the first 6 months after the enrollment. Only one half of the groups were symptomatic patients, who complained of cough, asthenia and loss of weight. Pulmonary infiltrative tuberculosis predominated among recruits. Extensive infiltrates and involvement of both lungs were identified in a lower proportion. The high rate of successful treatment outcome was endangered by the high rate of lost to follow-up patients, demonstrating poor evaluation and follow-up after the discharging from the hospital.
Conclusions: The epidemiological studies among military recruits are limited. The high rate of young, economically vulnerable men with risk factors demonstrates their priority for active screening. Treatment outcomes must be improved by the implementation of the adequate follow-up after hospital discharging.

Key words: tuberculosis, military, risk groups.

Introduction

Tuberculosis (TB) represents a major threat for health protection in the military forces worldwide [3]. The incidence of TB in the military forces is unknown. Military life consists in living, training, fighting in close quarters [14]. Military recruits are deliberately physically and mentally stressed during the training [1]. Continuous stress and associated harmful habits (e.g. tobacco smoking) could endanger the recruit's healthy state and contribute to the illness development [3]. In the United States (U.S.) military population's risk to develop tuberculosis was established eight times higher than in the general population [14]. Although, the estimated incidence of tuberculosis is unrecognized, the late detection and inadequate treatment put the members of the military forces at high risk [15]. World Health Organization (WHO) recommends stratifying the population according to the country specific profile for a better disease control [16]. The typical risk stratification is based on several criteria differentiated in low, mean and high impact risk factors, which should be used in the evaluation of each person before recruiting or each suspected case for tuberculosis [17]. The major risk factor identified in the (U.S.) military forces represents the recruits born in a high tuberculosis burden country or immigration from burden regions within 5 years from the arrival, and thus their health surveillance is important [15]. One of the most important factors associated with recrudescence of tuberculosis represents the latent tuberculosis infection (LTBI) assessed through the tuberculine skin testing (TST). The rate of positive TST was established two times higher in the American militaries than in the general population and higher in the American naval forces than in the army and air forces [14]. For improving the LTBI diagnosis there were recommended several commercially available interferon-gamma releasing assays (IGRAs): QuantiFERON-TB Gold and T-Spot TB test. However, the high rate of false-positive IGRAs results limits the usefulness in the LTBI and disease diagnosis [5, 20]. Other high risk factor for tuberculosis in military personnel is the HIV-infection or other immunocompromising conditions. According to the Moldovan national regulation the candidates for the incorporation in the military service should be investigated by clinical (physical examination) and laboratory methods during the health expertise performed by the medical military commission (MMC) [12]. The tuberculosis screening in military personnel is standardised and consists in medical history, physical examination and chest radiography [8, 12]. The capacity to perform military service is given by the excluding of well specified chronic diseases: HIV-infection, tuberculosis, diabetes, conditions requiring long-lasting immune suppressive treatment, cardiac diseases, arterial hypertension, renal diseases, central and peripheral nervous system diseases, psychiatric disorders, gastrointestinal disorders (chronic hepatitis, chronic malabsorption syndrome, chronic pancreatitis), low body weight and injection drug use [12]. Comparing the regulation papers, in the U.S. the militaries are investigated annually and are asked to answer some questions about: a) the face-to-face contact with someone sick with tuberculosis, b) place of birth and the presence of the family members outside the U.S., c) if the person had positive TST results or was previously treated for tubercu-

losis, d) if the persons worked or lived in a detainee facility, prison, homeless shelter, refugee camp or drug treatment facility, d) if the persons had an organ transplant, requires immunosuppressive medication (immune modulators or prednisone), had cancer of the head and neck, Hodgkin's disease, leukemia, end-stage renal disease, intestinal by-pass or gastrectomy [15]. A major attention is paid to the disease control among U.S. military health care workers. The U.S. health care workers caring the militaries are compulsory investigated if they: a) have the following symptoms: cough more than 2 weeks, fever more than 2 weeks, night sweats and weight loss; b) were working in an emergency room, inpatient hospital settings, mycobacteriology laboratory or other settings where tuberculosis patients are investigated and treated; c) had face-to-face contact with a sick person with tuberculosis and d) had written documentation of a prior positive TST, tuberculosis diagnosis and treatment [15].

Standard methods are used worldwide to detect tuberculosis in military population. Acid-fast bacilli sputum smear staining and culture on the conventional liquid or solid media are performed to each suspected person. This requires collecting at least two sputum samples in 8-24 hour intervals and one of which should be an early morning specimen [11]. However, the poor sensitivity (<30% in MD, <50% in the U.S.) of smear staining and delay of culture results (requires at least 120 days for providing a positive result) endanger the disease control in a military population [17]. Close contact between military personnel and their high receptivity to the infection make compulsory the performing the nucleic acid amplification testing in the frame of the case investigation. GeneXpert MTB/Rifampicine (Cepheid, California) represents a method extremely useful with a rapid capacity (2 hours) to detect *Mycobacterium* DNA and Rifampicin resistance mutations of the *rpoB* gene. It plays a decisive role in the treatment, allowing the onset of the treatment for multidrug-resistant infection before the results of the drug sensitivity test are available [7]. The U.S. Centre for Disease Control (CDC) recommends the use of IGRAs and TST for LTBI diagnosis. However, CDC requires that the results should be evaluated according to the patient's risk factors for infection and for developing the active disease. In the U.S. military settings several epidemics of TST conversions (prior negative than positive TST) were reported, but were attributed to the errors in the administration and reading of TST and cross-reactivity with non-tuberculosis mycobacteria [14].

The WHO's guideline for the treatment of tuberculosis is strongly recommended to be used in the settings caring sick military personnel [15]. The treatment must be performed as directly observed therapy (DOT) only in health care settings and the sick military person should be isolated until they have met the following criteria: 1) treatment with an effective regimen for at least 2 weeks; 2) two negative sputum smear at the end of the treatment's intensive phase; 3) clinical improvement during the treatment. The sick military personnel should be isolated in a negative pressured room and all infection control measures used [6, 15, 18].

The standard treatment for new patients presumed or known to have drug-susceptible tuberculosis is performed since 1993 and lasts 6 months [18]. It consists in a two phase regimen with four first-line drugs: isoniazid (H), rifampicine (R), ethambutol (E) and pyrazinamide (Z) used in the intensive phase and two first-line drugs: isoniazid and rifampicine used in the continuation phase. Previously sick patients have to be treated during 8 months with the same two phase regimen consisted of five first-line drugs: H, R, E, Z and streptomycine (S) in the intensive phase for 3 months followed by the continuation phase with H, R and E during the next 5 months. One of the emerging challenges in the treatment of tuberculosis in military forces is the epidemic extension of drug-resistance strains of *Mycobacterium.* Multidrug-resistant tuberculosis (MDR-TB) means the resistance to at least two of the most powerful first-line bactericidal drugs: isoniazid and rifampicine. An associated resistance to second-line drugs such as aminoglicozides (amikacyne, kanamycin and capreomycine) and any fluoroquinolone (levofloxacine or moxifloxacine) associated with multidrug-resistance was called extensively drug-resistant tuberculosis [22]. Military members are at a greater risk to become infected with drug-resistant strains circulating within the outbreaks from the quarters, but higher during the military service or overseas travel in the TB-endemic countries [10]. Usually patients identified with rifampicine-resistant strains or MDR-TB are treated with the standard combination of the second-line drugs for 18- 24 months (DOTS-Plus regimen) or different combinations (individualized regimens). The MDR-TB treatment success rate is low. It is associated with significant adverse events and poor treatment compliance [22]. In the Republic of Moldova the anti-tuberculosis treatment in military personnel is performed in specialized clinical departments during the intensive phase and in ambulatory at the home residence conditions in the continuous phase [4].

Reviewing exposed information it can be proved that tuberculosis, as a communicable, infectious disease is endangering the health protection in military forces all over the world. The rate of tuberculosis among millitary personnel is unknown, but the risk of infection and disease developing is much higher than in the general population. Reactivation of the latent tuberculous infection represents one of the most important factors for tuberculosis development in foreign born or immigrated persons from endemic countries; however, infection with drug-resistant strains is higher in outbreaks and during overseas military service. Case-management could be improved by performing cohort investigations, education of the military population about the clinical signs, detection procedures and using molecular genetic assays in all suspected cases. Treatment outcome could be improved by implementing an adequate patient's follow-up and evaluation.

The aim of the study was the assessment of the risk factors, clinical presentation and treatment outcome of tuberculosis in military recruits. The established objectives were: 1. assessment of social, economical and epidemiological risk

factors for tuberculosis in military recruits; 2. evaluation of the case-management, clinical and radiological aspects, microbiological results and treatment outcomes in military recruits.

Material and methods

According to the regulatory documents the military service of the Moldovan citizens in the National Armed Forces is performed in the frame of the National Army and Carabineer Troops during a limited period of time. The military service is performed compulsory by the citizens enlisted into the military service in term during 3 months (short contract), one year or more as specified time in the contract (variable contract).

It was performed a retrospective selective, descriptive study targeting risk factors, clinical aspects, laboratory results and treatment outcome of 51 patients – military recruits from the Chisinau Carabineer Troops diagnosed with tuberculosis in the period 01.01.2010-31.1201.2015. The inclusion criteria were: young age (18-24 years old) and signed informed consent. The study schedule included demographic, social, economical and epidemiological data, clinical features and laboratory results. All selected patients were diagnosed and managed according to the National Clinical Protocol 123 "Tuberculosis in adults". Statistic assessment was carried out using the quantitative and qualitative research methods. Statistical survey was performed using Microsoft Excel XP soft.

Results and discussion

All patients enrolled in the study were men. When distributing patients in age groups was established that the youngest group (18-20 years old) was the largest – 45 (88.23%) patients. Assessing the patients' residence was established that most of them were from the rural localities of the republic– 46 (90.19%) cases. No homeless patients were identified among selected cases. Distributing patients according to the educational level, it was determined that low level of school education (incomplete secondary school) was identified in every fourth case (13 (25.49%) patients), graduated lyceum one half of the group [25 (49.02%) patients], professional or superior studies had 9 (17.64%) patients.

Distributing patients according to the economical status it was established that the rate of employed patients before the recruitment was very low [4 (7.84%) patients]. History of migration in the last year was established in 2 (3.92%) patients. Every third patient [38 (74.51%) patients] was living under the standard of minimum consumption basket. Assessing the marital status it was identified that the majority of the patients [47 (92.16%) patients] were single-state persons due to their young age. Harmful social habits such as active tobacco smoking was established in one half of the group (25 (49,02%) patients) and alcohol abusers were 6 (11.76%) patients. No drug users were identified.

The proportion of patients with epidemiologic risk factors was low. Only 8 (15.68%) patients were from family infectious clusters, among them, 4 (7.84%) patients were in contact with drug-resistant tuberculosis family members and 3 (5.88%) patients were from clusters where a dead person due to tuberculosis was registered. Were previously treated for tuberculosis 12 (23.53%) patients and were diagnosed with post-tuberculosis lung changes 2 (3.92%) cases.

The rate of uninsured patients before recruitment was high [47 (92.16%) cases]. Diagnosis of tuberculosis was delayed for more than 60 days from the onset of the symptoms in 22 (43.14%) cases. Acute onset of tuberculosis was identified in 14 (27.45%) patients. 27 (52.97%) patients complained of the symptoms of the intoxication syndrome. Asthenia and loss of weight were identified in 27 (52.97%) patients, night sweats in 25 (49.02%) cases, fever in 4 (7.84%) cases, headache in 4 (7.84%) cases, loss of consciousness in 2 (3.92%) cases. Bronchopulmonary signs were established in 28 (54.91%) cases: cough for more than 3 weeks in 28 (45.91%) cases, thoracic pain in 5 (9.81%) cases, dysphagia in 2 (3.92%) cases and heamopthysis in 1 (1.96%) case. Associated diseases were diagnosed in 3 (5.88%) patients. No HIV infection, diabetes, immunosuppressive treatment and psychiatric disorders were identified.

Within the first 3 months after the enrollment 10 (19.61%) recruits developed tuberculosis and after the next three months – 16 (31.37%) recruits. During the first three months of the second semester 12 (23.53%) recruits developed active tuberculosis and three months later – 25.49%) patients (fig.).

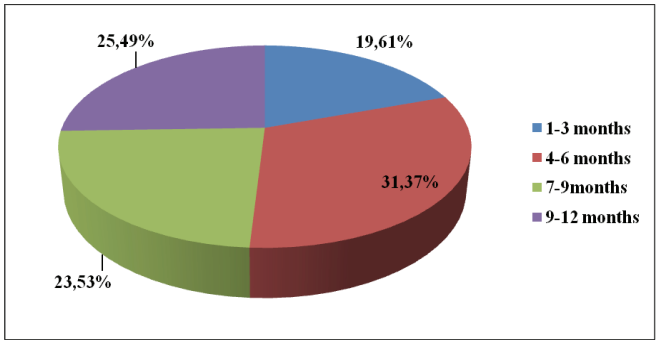

Fig. 1. Duration between enrollment and disease diagnosis (%).

The large spectrum antibiotherapy was initiated before tuberculosis treatment in 11 (21.57%) patients. When assessing the high risk factors, their hierarchy was established: patient's rural residence, unemployment before recruiting and harmful habits. The epidemiological risk factors such as household tuberculous contact and history of recent migration were identified in a low proportion, but it is important to emphasize the role of such factors in the infection and disease progression. Patients with comorbidities were in a limited number due to clear prohibiting conditions for the enrollment specified in the national regulatory documents (fig. 2).

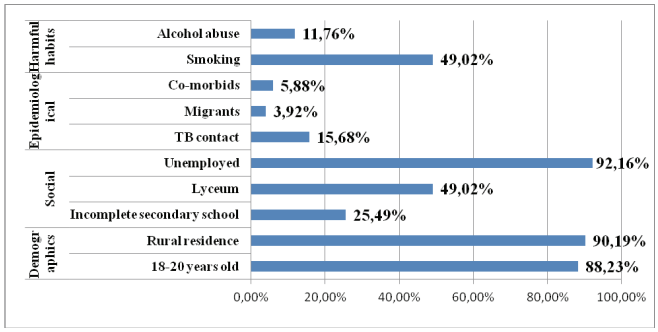

Fig. 2. Distribution of military recruits in risk groups (%).

Evaluating the laboratory features of the selected patients it was identified that 9 (17.64%) patients had positive results at the microscopic testing for acid-fast-bacilli and 8 (15.67%) had positive culture on solid Lowenstein-Jensen or liquid media (MGIT BACTEC). The first-line anti-tuberculosis drugs susceptibility was established in 6 (11.76%) cases, mono-resistance in 2 (3.92%) cases and multidrug-resistance in 1 (1.96%) case.

When assessing the radiological features of selected patients it was established that the patients with one affected lung outnumbered those with both involved lungs [38 (74.51%) vs. 13 (25.49%) cases, p<0,001]. Right superior lobe was affected in 21 (41.18%) cases and left superior lobe in 14 (27.45%) cases. Tuberculosis of the right lung was diagnosed more frequently than in the left lung: 29 (56.86%) patients compared to 22 (43.14) patients. Extensive infiltrates involving more than 3 segments were established in 12 (23.53%) cases and lung destruction was identified in 9 (17.64%) cases. The greatest part of the group was diagnosed with infiltrative form of pulmonary tuberculosis – 43 (84.31%) patients. Limited forms, recognized as nodular tuberculosis were diagnosed in 5 (9.81%) cases. It is important to note the absence of cases with severe forms, such as disseminated or fibro-cavernous tuberculosis. Secondary localizations were diagnosed in a low proportion: pleurisy – 3 (5.88%) patients and tuberculosis of the bronchus – 2 (3.92%) patients. Extrapulmonary form, such as tuberculosis of intrathoracic lymph nodes was diagnosed in 2 (3.92%) patients. Data were revealed in the figures 3 and 4.

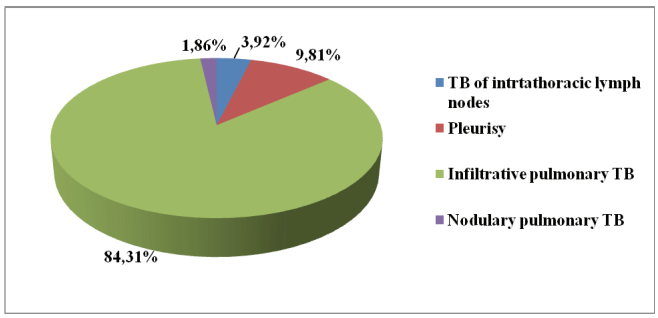

Fig. 3. Established clinical diagnosis in military recruits (%).

Comparing obtained results with previously published studies in the national journals it can be demonstrated that pulmonary tuberculosis was established in a similar rate as in the general population [9]. However, the rate of extensive infiltrates associating lung destruction and involvement of both lungs was much lower than in the general population.

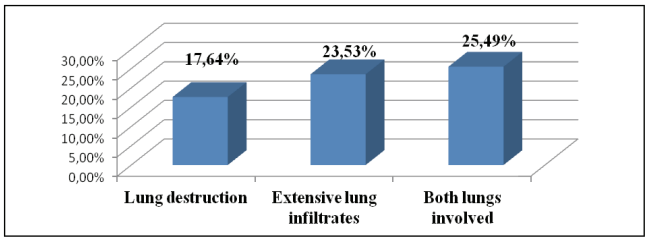

Fig. 4. Radiological features of pulmonary tuberculosis in military recruits (%).

As a consequence the proportion of positive microbiological results, which included smear microscopy and culture in the conventional media, was very low (fig. 4).

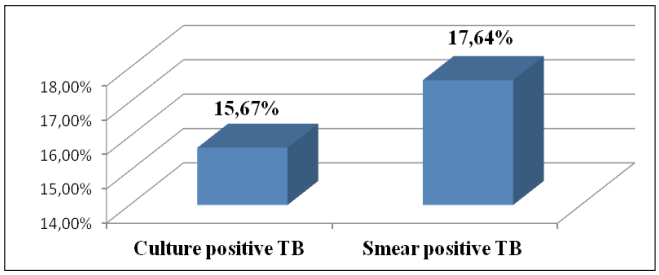

Fig. 5. The proportion of microbiological positive results.

All patients were treated during the intensive phase in the Chisinau Municipal Hospital of Pneumophtysiology. One half of the group [25 (49.02%) patients] was hospitalized for 2 months in the Municipal Hospital of Tuberculosis, 7 (13.72%) patients were hospitalized on average 3 months and 19 (37.25%) patients – more than 3 months. Treatment for MDR-TB was performed in 3 (5.88%) patients. Successfully treated according to the national policy criteria were 41 (80.39%) patients, that included 18 (35.29%) cured and 23 (45.10%) with completed treatment, 9 (17.64%) were lost to follow-up and 1 (1.96%) patient failed the treatment. The follow-up till 2016 of the selected group identified that 14 (27.46%) patients were included in retreatment regimens (fig. 3).

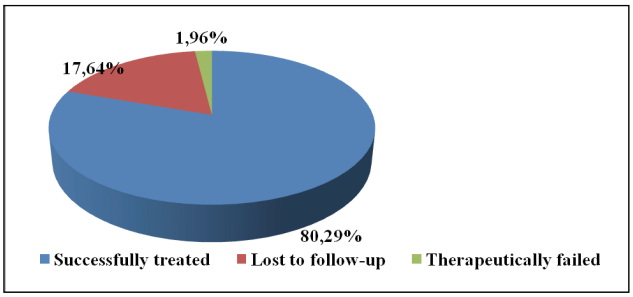

Fig. 6. Final treatment outcomes (%).

Conclusions

Moldovan citizens perform military service in the National Army or Carabineer Troops during different periods, specified in the contract.

In the Chisinau Municipal Clinical Hospital were diagnosed and treated 51 military recruits in the period 2010-2015.

All were men. Most of them were aged between 18-22 years old and were from rural localities of the republic. Every fourth had low level of the school degree and one half graduated the lyceum.

Before recruiting most of the patients had an economical vulnerable state, lacked the health insurance and were single-state persons. Obtained results demonstrated that military recruits had low accessibility to health care services due to their social vulnerability.

One half of the group comprised active smokers. Every fourth patient had tuberculosis in the childhood. Family contact with a sick person and the history of migration were established in a small number of cases.

Disease's insidious onset was established in one half of the group and acute onset in every fourth patient. Every tenth patient was diagnosed with tuberculosis within the first 6 months after the enrollment in the military service.

Cough, asthenia and loss of weight were established in all symptomatic cases, which constitute one half of the group.

Pulmonary forms of tuberculosis were the most prevalent, although extrapulmonary forms as pleurisy and tuberculosis of intrathoracic lymph nodes were diagnosed as well. Extensive infiltrates and involvement of both lungs were identified in a lower proportion than in the general population. No severe forms were diagnosed. Comorbidities were diagnosed in a limited number of cases at the same time with tuberculosis.

High rate of successfully treated militaries was endangered by a high rate of the lost to follow-up patients, demonstrating poor control after the discharging from the hospital and the military service.

The epidemiological data on tuberculosis among Moldovan military forces is unknown. The high rate of young, economically vulnerable men with risk factors demonstrates their priority for active screening.

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Metabolism and physiological effects of carbon dioxide. Implications in anaesthetic management

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Abstract

Background: Carbon dioxide is a normal by-product of aerobic metabolism that maintains the equilibrium of respiratory act, being eliminated from the lungs. Despite of an increasing number of researches concerning carbon dioxide metabolism and its effects on human homeostasis, there are still discussions about carbon dioxide metabolism, physiology and its implication in anaesthetic management, ICU, critically ill patient. The use of mild to moderate hypercapnia during general anaesthesia and in mechanically ventilated patients is growing, based on scientifical researches of last years.
Material and methods: There has been scientifically evaluated data from PubMed, 2002-2017. Key words used in search are: "carbon dioxide", "ventilation", "metabolism", "gas change". There were selected articles, taking in consideration their title, and chosen abstracts. The article contains a qualitative analysis and synthesis of the recommendation, concerning anaesthetic management and metabolism of carbon dioxide.
Conclusions: Carbon dioxide metabolism and its anaesthetic management, represents a challenge that will be actual for many years in future. The amount of controversial studies about effects of carbon dioxide on patients under general anaesthesia or mechanical ventilation, determined us to perform a review of literature, and evaluate it.
There are known facts about carbon dioxide metabolism, such as normal values, how it is produced in human body, how it is evacuated, effects on cardiovascular, nervous systems, and still there are many controversial studies on that topic, that determine to study it more and find new research results.
Key words: carbon dioxide, ventilation, metabolism, gas change.

Introduction

Arterial carbon dioxide tension represents the balance between the production and elimination of carbon dioxide, and in healthy persons, it is maintained within narrow physiologic limits. $EtCO_2$ represents the partial pressure or maximal concentration of carbon dioxide (CO_2) at the end of an exhaled breath, which is expressed as a percentage of CO_2 or mmHg [3-6]. The normocapnic values are 5% to 6% CO_2, which is equivalent to 35-45 mmHg. CO_2 reflects cardiac output (CO) and pulmonary blood flow as the gas is transported by the venous system to the right side of the heart and then pumped to the lungs by the right ventricles [3,4]. When CO_2 diffuses out of the lungs into the exhaled air, a capnometer measures the partial pressure or maximal concentration of CO_2 at the end of exhalation.

Carbon dioxide being a by-product of aerobic metabolism, has a significant role in ventilation process of lungs. For many years CO2 was considered a harmfull metabolit that was no need to be maintained in human organism, so hypocapnia was maintained during general anaesthesia. It was considered that hypocapnia with induced vasoconstriction provided during general anaesthesia, from economical reasons was beneficial. Only during past ten years, it was determined that mild to middle hypercapnia induced to patients that suffer of acute respiratory distress syndrome (ARDS), resulted in significant improvement of their medical condition. After a few studies concerning effects of hypercapnia, the interest to this topic started to grow. Nowadays, there is increasing amount of studies about effects of mild to middle hypercapnia for the Intensive Care Unit (ICU) patients or effects of hypercapnia during general anaesthesia.

Material and methods

The article contains a scientific review of carbon dioxide metabolism from PubMed that was published in 2002-2017. There were selected prospective studies, guidelines, textbooks of respiratory physiology, and anaesthetic management. Key words used in search are: carbon dioxide, ventilation, metabolism, gas change. The article contains a qualitative analysis and synthesis of the recommendations, concerning anaesthetic management and metabolism of carbon dioxide. There were selected articles, taking in consideration their title, and chosen abstracts. In the process of searching by title using the key word, there have been found 3200 results. After selecting period of years 2002-2017, 737 results appeared.

Results

Carbon dioxide (CO_2) is a normal by-product of aerobic metabolism in human body (fig. 1). Increased CO_2 in the body results in important physiological responses throughout the body. CO_2 is a potent stimulus of pulmonary minute ventilation and it acts by stimulating chemoreceptors in the carotid bodies and respiratory control centres in the brain and brainstem, that change in ventilation in response to CO_2 production that keeps alveolar pressure of CO_2 (PCO_2) in dynamic equilibrium with metabolically produced CO_2 [2,3]. Carbon dioxide is also a potent stimulus of cerebral vasodilation and blood flow.

Hypercarbia can result from hypoventilation: low breathing rate allows build-up of CO_2 (e.g., deliberate "skip-breathing" by SCUBA divers), malfunctioning respirator can lead to increased rebreathing of CO_2, increase in the dead space of breathing apparatus or increased alveolar dead space (e.g.,

pulmonary embolism), increased breathing resistance of respiratory protective device (RPD) leading to a reduction in breathing frequency.

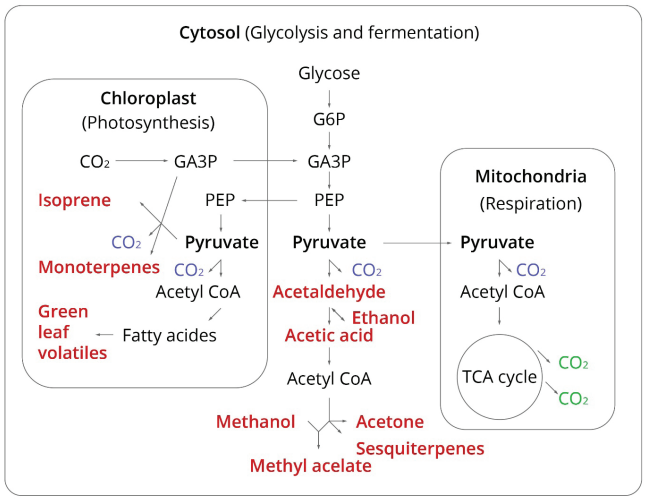

Fig. 1. Aerobic metabolism in human body, according to slideshare.com.

In addition, a high CO_2 in human body can induce visual disturbances, headache, and reduction in reasoning ability, a sense of "air hunger" or dyspnoea.

Elevated level of CO_2 in human blood can act as an anaesthetic and can cause unconsciousness inducing inert gas narcosis similar to nitrous oxide. CO_2 can alter the intracellular pH thus having effects on metabolism (also probable mechanism for inert gas narcotic effect) [8, 9, 10]. In its simplest form, the partial pressure of arterial carbon dioxide ($PaCO_2$) reflects the balance between the production and elimination of carbon dioxide (CO_2), as described by the following formula:

$$PaCO_2 \text{ is proportional to } \frac{CO_2 \text{ production}}{CO_2 \text{ elimination}} + \text{inspired } CO_2.$$

End tidal Co_2 ($EtCO_2$) represents the partial pressure or maximal concentration of CO_2 at the end of exhalation. CO_2 reflects cellular metabolism. There are four main stages of normal physiology of CO_2: production, transport, buffering and elimination.

Production: CO_2 is a metabolic by-product of aerobic cell metabolism. As the intracellular CO_2 increases, CO_2 diffuses out into the tissue capillaries and is carried by the venous circulation to the lungs, where it diffuses from pulmonary capillaries into the alveoli. The partial pressure of CO_2 of venous blood entering pulmonary capillaries is normally 45 mmHg; the partial alveolar pressure of CO_2 ($PACO_2$) is normally 40 mmHg [6]. The pressure difference of 5 mmHg will cause all the required CO_2 to diffuse out of pulmonary capillaries into the alveoli.

Transport: The second stage is CO_2 transport, which is a way of maintaining the CO_2 tension of arterial blood at approximately 35-45 mmHg despite high CO_2 production.

Buffering: The third stage is where the buffer action of haemoglobin and pulmonary blood flow maintain the normal level of CO_2 tension by eliminating the excess $CO_{2.\ CO2}$ can either be carried, dissolved or combined with water (H_2O) to form carbonic acid (H_2CO_3), which can dissipate to hydrogen ions (H+) and bicarbonate ions (HCO_3-): (CO_2 + H_20 <=> H_2CO_3 <=> H+ HCO_3-). The hydrogen ions are buffered by haemoglobin, and the bicarbonate ions are transported into the blood. This mechanism accounts for 90% of CO_2 transport.

Elimination: The fourth stage involves CO_2 elimination by alveolar ventilation under the control of the respiratory center. This process allows the diffusion of CO_2 from blood to the alveoli where the partial alveolar pressure of CO_2 is lower than the tissue pressure [10, 11].

During normal circulatory condition with equal ventilation/perfusion ratio (V/Q) relationship, $PACO_2$ is closely comparable to $PaCO_2$ and $EtCO_2$; therefore, $PaCO_2$ is equivalent to $EtCO_2$. The difference between $PaCO_2$ and $EtCO_2$ is known as the CO_2 gradient [13-15]. The normal $EtCO_2$ is about 38 mmHg at 760 mmHg of atmosphere with less than 6 mmHg gradients between $PaCO_2$ and $EtCO_2$.

The principle determinants of $EtCO_2$ are: alveolar ventilation, pulmonary perfusion (cardiac output) and CO_2 production.

During acutely low cardiac output state as in cardiac arrest, decreased pulmonary blood flow becomes the primary determinant resulting in abrupt decrease of $EtCO_2$ [16, 18]. Changes in alveolar ventilation can also influence $EtCO_2$ as $PACO_2$ closely approximates $PaCO_2$ and $EtCO_2$. If ventilation and chest compressions are constant with the assumption that CO_2 production is uniform, then the change in EtCO2 reflects the changes in systemic and pulmonary blood flow. Ultimately, $EtCO_2$ could be used as a quantitative index of evaluating adequacy of ventilation and pulmonary blood flow during CPR.

Monitoring the carbon dioxide metabolism during general anaesthesia represents a key-factor in managing an adequate anaesthesia. A lower level of $EtCO_2$ than 35 mmHg is being considered hypocapnia [17,18,19]. A level of $EtCO_2$ 35-45 mmHg is determined as normocapnia, and levels more than 45 mmHg, are considered hypercapnia.

Hypocapnia has been considered during general anaesthesia for the purposes of suppressing respiratory effort and reducing anaesthetic requirements. Hypocapnia and associated alkalosis, however, have physiological effects that may be detrimental. Such effects include decreased cerebral blood flow and cognitive function, increased airway resistance and pulmonary cellular dysfunction, vasoconstriction and increased myocardial oxygen demand, hypercoagulability, and dysrhythmias. In contrast, hypercapnia may have beneficial effects including increased cardiac index, oxygen delivery and tissue (e.g. surgical site) oxygen tension, and attenuation of lung injury. As these effects may influence postoperative complications, postoperative recovery, or both, there could be a relationship between intraoperative end-tidal carbon dioxide (EtCO2)

and clinical outcomes [19]. Moderate to severe hypocapnia (partial pressure of arterial carbon dioxide, 20 to 25 mm Hg) was, an adjunct to general anaesthesia.

Its proposed advantages include the minimization of spontaneous respiratory effort and a reduced requirement for sedative, analgesic, and muscle-relaxant medications.

The latter advantage may explain the widespread use of intraoperative hyperventilation in the 1960s as a means of reducing the use of anaesthetic medications and thus avoiding fetal depression immediately after caesarean section. The use of hypocapnia during general anaesthesia remained common for at least the next two decades.

Hyperventilation and hypocapnia decrease cardiac output, which in turn decreases blood flow and oxygen tension in brain and splanchnic organs. Hypocapnia also shifts the oxyhaemoglobin curve leftward and restricts oxygen unloading at the tissue level [19].

Hypercapnia, in contrast, increases cardiac output and decreases systemic vascular resistance and oxygen extraction; it thus increases oxygen availability to tissue. Hypercapnia also causes a complex interaction between altered cardiac output, hypoxic pulmonary vasoconstriction, and intrapulmonary shunt with the result being a net increase in PaO_2 at a given inspired oxygen concentration. Consistent with these observations, we recently demonstrated that short periods of hypercapnia improve tissue oxygenation in anaesthetised volunteers.

Ventilation is the movement of gases between the atmosphere and the alveoli. This must be distinguished from oxygenation. While ventilation might be normal, oxygenation can be inadequate if either the gas inhaled is lacking in oxygen or perfusion to the pulmonary alveoli is compromised. Ventilation consists of two phases: inspiration and expiration. Inspiration delivers oxygen to the alveoli and expiration delivers carbon dioxide, the by-product of cell metabolism, to the environment [20]. Although ventilation can be initiated voluntarily, it is largely under the control of the respiratory centres of the medulla where chemoreceptors respond to elevations in hydrogen ion concentration (pH) in the following manner: Carbon dioxide (CO_2) diffuses from the blood to the cerebrospinal fluid in the brain and combines with water to form carbonic acid. The acid dissociates into bicarbonate and hydrogen ions ($CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$). Although the chemoreceptors actually respond to hydrogen ions, the mechanism is referred to as *hypercapnic drive* because it is activated as serum carbon dioxide tensions elevate. The respiratory centre can also be stimulated by neural impulses generated in the peripheral chemoreceptors of the aortic and carotid bodies. These receptors respond primarily to a decline in PaO_2, and they are referred to as *hypoxemic drive*. Normally this mechanism assumes a secondary role to central hypercapnic drive, but assumes greater significance when central receptors become tolerant to elevated CO_2 levels that occur with disorders such as chronic obstructive lung disease [20].

Like oxygen, the smallest portion of carbon dioxide in blood is in the free state. Most is transported as bicarbonate ion (70%), and 23% is bound to haemoglobin as carbaminohemoglobin. Only 7% of total carbon dioxide is dissolved in blood and produces a gas tension, designated $PaCO_2$. Normal $PaCO_2$ is approximately 40 mm Hg, and it can be measured in arterial blood gas studies along with PaO_2, as described above.

While PaO_2 is used to assess oxygenation, $PaCO_2$ is the true measure of ventilation. As stated above, ventilation may be normal but the patient can be hypoxemic if the gas inhaled is deficient in oxygen or pulmonary perfusion is compromised. Conversely, a patient who is hypoventilating may be well oxygenated if he or she is breathing a gas mixture enriched with oxygen. However, $PaCO_2$ will invariably elevate if ventilation is inadequate because carbon dioxide is not being eliminated. To summarize, a low PaO_2 indicates poor oxygenation (hypoxemia) while an elevated $PaCO_2$ (hypercarbia) indicates hypoventilation [21].

Capnometry is the measurement of carbon dioxide concentration during the respiratory cycle. It uses infrared technology to analyse carbon dioxide in exhaled gas. There are multiple options to facilitate sampling of carbon dioxide. The most accurate readings are those obtained by sampling gases in the endotracheal tube of an intubated patient. However, during moderate and deep sedation the patient is not intubated, so other devices have been developed for gas sampling. Special nasal cannulas, designed to provide supplemental oxygen during sedation, also have a sampling line included. Cannulas without this feature can be modified by placing an intravenous catheter through one of the nasal prongs and attaching the monitor sampling line to the catheter hub [22].

Capnography is the proper term for those monitors that display a continuous waveform reflecting inspiration and expiration. While capnometers and capnographs both display numeric values for $EtCO_2$ and respiratory rate, capnography is preferred because visualization of the waveform allows continuous assessment of the depth and frequency of each ventilatory cycle. Respiratory depression produces a reduction in number of waveforms while obstructions alter the shape and height of each waveform [20, 21].

Discussion

Intraoperative hyperventilation to induce hypocapnia has historically been common practice and has physiological effects that may be detrimental. In contrast, hypercapnia has effects that may be beneficial. As these effects may influence postoperative recovery, was investigated the association between variations in intraoperative carbon dioxide and length of hospital stay in patients who had elective colon resections and hysterectomies. There was a significant association between higher intraoperative $EtCO_2$ and shorter LOS after colon resection and open hysterectomy [22]. Also hypercapnia, increases cardiac output and decreases systemic vascular resistance and oxygen extraction; it thus increases oxygen availability to tissue. Hypercapnia also

causes a complex interaction between altered cardiac output, hypoxic pulmonary vasoconstriction, and intrapulmonary shunt with the result being a net increase in PaO_2 at a given inspired oxygen concentration. Consistent with these observations, recently demonstrated that short periods of hypercapnia improve tissue oxygenation in anaesthetised volunteers [3].

Hypercapnic acidosis, common in mechanically ventilated patients, has been reported to exert both beneficial and harmful effects in models of lung injury. Study on effects of hypercapnic acidosis on mitogen-activated protein kinase (MAPK) activation, determined that p44/42 MAPK activation in a murine model of ventilator-induced lung injury (VILI) correlated with injury and was reduced in hypercapnia models [23].

Continuing studies on effects of carbon dioxide, in anesthesic management of patients, may improve the quality of perioperative management. The outcomes could open new strategies for anaesthetic management and critically ill patients with pulmonary disease, considering mechanical ventilation.

Conclusions

Metabolism of carbon dioxide is a part of respiratory physiological act. There are known facts about carbon dioxide metabolism, such as normal values, how it is produced in human body, how it is evacuated, effects on cardio-vascular and nervous systems, and still there are many controversial studies, that determine to study more and find new research results.

Whereas oxygen is necessary for life and vital for aerobic metabolism, and carbon dioxide is a normal product of aerobic metabolism and is an important regulator of physiological function.

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Overview of evolution of premature mortality from major cardiovascular diseases in the Republic of Moldova, 2003-2015

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Abstract

Background: Cardiovascular disease is the leading cause of mortality at the global and national level. Ischeamic heart diseases, cerebrovascular diseases and hypertensive heart disease together identify a highest proportional mortality that defines them as major contribution cardiovascular diseases worldwide. Premature mortality analyzing compared to traditional moves target from classical focus on the occurrence of deaths to focus on the losses caused by these deaths. The purpose of the study is to assess the premature mortality evolution from major cardiovascular diseases among adults in the Republic of Moldova for the period of 2003-2015.

Material and methods: the research is a descriptive population study over the time of 13 years. The premature mortality phenomenon was counted in the years of potential life lost (YPLL). Age-adjusted rates were calculated using the direct method of standardization applying WHO World Standard Population Distribution (%) based on world average population between 2000-2025.

Results: Overall period from 2003 to 2015, premature mortality rate from ischeamic heart diseases (+10.7%) and hypertensive heart disease (+41%) have registered increasing trends versus premature mortality rate from cerebrovascular diseases with decreasing trend (-23.9%). All together determined the decreasing trend (-2.4%) of major cardiovascular diseases premature mortality rate. When analyzing percentage changes of premature mortality increasing trends by age, the study findings identified the higher percentage changes in younger groups for ischeamic heart diseases premature deaths than hypertensive heart disease.

Conclusions: Despite the general decreasing trend of major cardiovascular diseases premature mortality rate, ischemic heart diseases compared to cerebrovascular and hypertensive heart disease identify the most pronounced trends of the deaths event rejuvenation in the Republic of Moldova for the period 2003-2015.

Key words: cardiovascular disease, premature mortality, years of potential life lost.

Introduction

Cardiovascular diseases are identified as the leading cause of mortality at the global level [1, 2, 3, 4] and national level, as well [5, 6]. Ischeamic heart disease, cerebrovascular diseases and hypertensive disease are referred by World Health Organization (WHO) as major cardiovascular diseases due to their high proportional mortality contribution [1, 2]. In the Republic of Moldova major contribution cardiovascular diseases are a part of 96.6 %, compared to 85% estimated on the global level in 2011 [1,2,7].

Unlike the traditional analyzing of mortality phenomenon, statistical indicator Years of Potential Life Lost (YPLL), proposed by the Global Burden of Disease 1990 study to estimate the burden of disease in a population [8], moves target from classical focus on the occurrence of deaths to focus on the losses caused by these deaths [7, 9]. The World Health Organization notes that the majority of premature deaths are avoidable, underlining the importance of a 25% reduction of premature mortality from noncommunicable diseases by 2025 in the world [2, 10]. In addition, the event of premature death is recognized as basic point of population health assessment [11, 12, 13], along with economic impact evaluation [14].

Aligning to the global efforts to prevent and control non-communicable diseases, including cardiovascular diseases, the Government of the Republic of Moldova has undertaken to reduce the avoidable burden of non-communicable diseases and risk factors for the years 2012-2020, adopted in the legislative and normative documents at the country level [15,16]. Relative reducing (10%) of premature mortality from cardiovascular diseases is one of the targets of the Republic of Moldova by 2020 in terms of control and prevention of noncomunicable diseases [17, 18].

The study purpose is to assess the premature mortality evolution from major cardiovascular diseases for the period of 2003-2015 in order to highlight their impact on the population health in the Republic of Moldova.

Material and methods

The research design was a descriptive population study in terms of premature mortality evolution for the period from 2003 to 2015 in the Republic of Moldova. The primary source of data collection was death certificate (form No 106/e) approved for application in the country since 2004. There were considered all deaths cases registered by the National Center of Health Management in collaboration with National Bureau of Statistics of the Republic of Moldova overall period 2003-2015 [5, 6].

The premature mortality phenomenon was counted in the years of potential life lost (YPLL) according the following formula (1):

$$YPLL = \sum_{i=1}^{n} d_i(70 - a_i) \quad (1)$$

Where:

n – Number of five years age groups;

d_i – Number of deaths in each five years age group;

70 – End point age;

a_i – Midpoint interval of each five years age group.

The rate of premature mortality (YPLL Rate) was calculated according the formula (2):

$$\text{YPLL Rate} = \frac{\text{Number of IPLL}}{\text{Number of population under 70 years age}} \times 100.000 \quad (2)$$

Age adjusted premature mortality rate was calculated using the steps of direct method of standardization, which allows comparisons between the sexes and geographical areas by considering a conventional population assuming that the age structure is the same in both sexes. There was applied as a standard for years of potential life lost adjustment rates of the WHO World Standard Population Distribution (%) based on world average population between 2000-2025 [19].

Results

Major cardiovascular diseases (I20-I25; I60-I69; I11)

In 2015, major cardiovascular diseases registered 22,018 deaths that resulted in 61,448 potential years of life lost (PYLL). Major cardiovascular diseases caused about 66.9% of all deaths from noncommunicable diseases in the Republic of Moldova. Major cardiovascular diseases premature deaths were identified in a proportion of 38.9% from total noncommunicable diseases and 21.8% from all causes of deaths in 2015.

Diseases of the circulatory system are the leading cause in the all causes of proportional mortality rate (58%), structured in 95.6% (in 2015) by three clinical forms, as following: ischeamic heart diseases (62%), cerebrovascular diseases (25,3 %), and hypertensive heart disease (8.3%), referred as major cardiovascular diseases. Major cardiovascular diseases identified deaths under the age of 65 year in 19.3% (95% CI 18.8% - 19.8%), indicating that about one in five deaths is produced in premature age. Proportional mortality rate from major cardiovascular disease by gender determined 44.6% (95% CI 44.0% - 45.3%) for males and 55.4% (95% IC 54.7% 56.0%) for females. Along with the fact that the distribution of deaths under 65 years of age from major cardiovascular diseases registered a higher proportion for males 67.2% (95% CI 65.8% - 68.6%) compared to women 32.8% (95% IC 31.4% - 34.2%). The distribution of deaths from major cardiovascular diseases for men aged less than 65 years was 29.0% (95% IC 28.1% - 29.9%): approximately every third male's death from major cardiovascular diseases was in premature age. The distribution of deaths from major cardiovascular diseases for women aged less than 65 years was 11.4% (95% IC 10.9% - 12.0%): about one in nine deaths by major cardiovascular diseases in women were premature.

Age-standardized rates of premature mortality from major cardiovascular diseases were permanent higher for age group 40-64 years for the overall period 2003-2015, ranging from 1034.8 (in 2013) to 1406.2 (in 2005) per 100,000 population. Standardized rates of premature mortality from major cardiovascular diseases in total were decreasing from 1,648.1 to 1,321.7 per 100,000 population for the period from 2003 to 2015. Standardized rates of premature death by age from major cardiovascular diseases have been decreased for ages 40-64 (from 1331.1 to 1048.5 per 100,000 population) and over 65 years (from 170.3 to 120,8 per 100,000 population), along with it an increase of standardized rates was registered for group 18-39 years (from 141.7 to 149.6 per 100,000 population).

Adjusted rates were higher for men (ranging from 1932.8 in 2013 to 2475.7 in 2005 per 100,000 population) compared to women (ranging from 733.7 in 2015 to 1181.6 in 2003 per 100,000 population), including all age groups in question: 18-39; 40-64; 65+ years, and productive years of age. Over the period 2003-2015 standardized rates of premature mortality from major cardiovascular diseases have decreased for both sexes: in males from 2,202.6 to 1,995.1 and in females from 1,181.6 to 733.7 per 100,000 population. Age-adjusted rate of premature mortality from major cardiovascular diseases in males compared to women is 2.7 times higher (in 2015). Standardized rates of premature mortality from major cardiovascular diseases by gender and age have shown a decrease for the majority of age groups analyzed in males and females, except in the 18-39 age groups in males, which showed a relative increase from 198.4 to 220.5 per 100,000 populations.

From 2003 to 2015 percentage change in major cardiovascular diseases premature mortality rate registered decreasing trend in total (-2.4%), along with rising trend in males (+ 9.8%) and decreasing trend in women (-22%). In addition, there were found the rising percentage changes in premature mortality rate from major cardiovascular diseases only in age group 18-39 years (+20.1%) versus decreasing percentage changes trends in age group 40-64 years (-11%), age group over 65 years (-29.1%) and productive years age group (-7.6%) (fig. 1).

With the general description of the major cardiovascular diseases, it is very important the descriptive analysis by clinical forms, which are the component parts of major cardiovascular diseases phenomenon, as follows:

Ischeamic Heart Diseases (I20-I25)

Ischeamic heart diseases are the leading cause of mortality of men and women in the Republic of Moldova with an average of 15,407 annual deaths overall period 2003-2015, which in 19% (95% CI 18.4% - 19.7%) cases are deaths under 65 years of age. Along with, every fifth death from ischeamic heart diseases was in premature age, ischeamic heart diseases produced more than a half (62%) of deaths from the diseases of circulatory system and more than 1/3 of total annual deaths. In 2015, ischeamic heart diseases have counted a number of 14,275 cases which produced 39,832 potential years of life lost (PYLL). Proportion of premature deaths from ischeamic heart diseases was determined in 64.8% from major cardiovascular diseases and in 14.1% from all causes of deaths in 2015.

For the period 2003-2015 age-standardized rates of premature mortality from ischeamic heart diseases were permanently higher for age group 40-64 years, ranging from

670.7 (in 2011) to 806.9 (in 2005) per 100,000 population. Adjusted rates of premature deaths from ischeamic heart diseases in men were higher (ranging from 1309.1 in 2011 to 1579.2 in 2005 than in women ranging from 426.6 in 2011 to 616.1 in 2012 per 100,000 population), inclusively all analyzed age groups, as follows: 18-39; 40-64; 65+ years, and productive years of age.

The percentage change in premature mortality caused by ischeamic heart diseases for the period 2003-2015 showed growth trends for all age groups except the age group over 65 years. Rising trends of premature mortality were determined as +38.1% for age group 18-39, +2.9% for age group 40-64 years, and +4.8% for group of productive years age (fig.1).

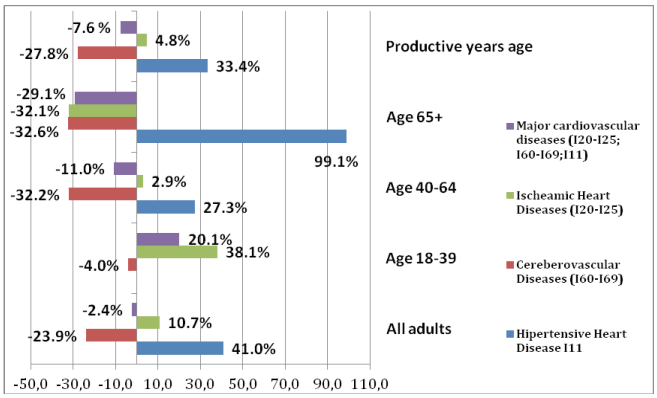

Fig. 1. Percentage change in major cardiovascular diseases premature mortality rates among adults, the Republic of Moldova, 2003-2015.

The increasing trends of percentage change in overall premature mortality from ischeamic heart diseases (+10.7%) was largely determined by the rising trends of premature mortality in men for all age groups. In addition, premature mortality rising trends for men were higher in younger age groups lying from + 38.2% for age group 18-39 years to + 13.0% for age group 40-64 years.

Cerebrovascular Diseases (I60-I69)

In 2015, cerebrovascular diseases recorded 5,835 deaths producing 19,302 potential years of life lost (PYLL). Cerebrovascular diseases were responsible for 31.4% of all PYLL from major cardiovascular diseases and a proportion of 7% from all causes of deaths in 2015.

Proportional mortality from cerebrovascular diseases by age was 22.8% (95% IC 21.8%-23.9%) in case of age groups under 65 years. In 2015, every fifth death from cerebrovascular diseases was in premature ages.

Age-standardized rates of premature mortality from cerebrovascular diseases were higher for age group 40-64 years overall period from 2003 to 2015, ranging from 320.9 (in 2013) to 563.3 (in 2005) per 100,000 population. Adjusted rates of premature mortality from cerebrovascular disease by gender were higher in case of men (ranging from 595.5 in 2012 to 837.6 in 2005) than in women (ranging from 258.3 in 2015 to 566.8 in 2005 per 100,000 population), inclusively all analyzed age groups, as follows: 18-39; 40-64; 65+; and productive years of age.

The percentage change of rates in premature mortality from cerebrovascular diseases for the period 2003-2015 registered decreasing trends for both men and women, with the exception of men aged 18-39 years with rising trend of +22.5%. The percentage change in premature mortality caused by cerebrovascular diseases for the period 2003-2015 showed decreasing trends for all age groups in question (fig.1). In addition, it was found that decreasing trend of percentage changes in premature mortality rates from cerebrovascular diseases for women was 3.6 times higher compared to men.

Hypertensive Heart Disease (I11)

In 2015, hypertensive heart disease recorded 1,908 deaths producing 2,312.5 potential years of life lost (PYLL), which determined 3.8% of total PYLL from major cardiovascular diseases.

Premature deaths from ischeamic heart disease were associated with hypertension in 21.2% of total premature deaths cases which were responsible for 9.4% of total potential years of life lost produced by this disease. Premature deaths from cerebrovascular disease were associated with hypertension in 40.7% of total premature deaths cases which were responsible for 30% of total potential years of life lost produced by this disease. Age-standardized premature mortality rates from cerebrovascular disease associated with hypertension identified higher frequencies compared to ischeamic heart disease associated with hypertension (1.9 times) and hypertensive heart disease (3.2 times).

Age-adjusted rates of premature mortality from hypertensive heart disease by gender registered higher level for men compared to women, respectively ranging from 38.0 (in 2012) to 61.8 (in 2014), and from 27.1 (in 2009) to 41.7 (in 2007) per 100,000 population. In addition, for both sexes the age group 40-64 years identified higher frequencies than age groups: 18-39; over 65, and productive years of age.

The percentage change of rates in premature mortality from hypertensive heart disease for the period from 2003 to 2015 recorded an increasing trend (+41%), along with a rising percentage for age group 40-64 years (+27.3%) and over 65 years (99.1%) (fig.1). Evolution of hypertensive heart disease by gender identified higher percentage change in women (+67.5%) than men (23.9%) overall period 2003-2015.

Discussion

Along with general decreasing trend of major cardiovascular diseases premature mortality rate (-2.4%) for the period 2003-2015, the study found when referring to every clinical form in question: ischeamic heart diseases, cerebrovascular diseases and hypertensive heart disease the trends of premature mortality rates were different. Overall period from 2003 to 2015, premature mortality rates from ischeamic heart diseases (+10.7%) and hypertensive heart disease (+41%) have registered increasing trends versus premature mortality rate from cerebrovascular diseases with decreasing trend (-23.9%).

When analyzing percentage changes of premature mortality increasing trends by age, the study findings determined the higher percentage changes in younger groups for ischeamic heart diseases premature deaths than hypertensive heart disease, respectively as following: age group 18-39 years (+38.1%), 40-64 years (+2.9%) , over 65 years (- 32.1%) and age group 18-39 years (a small number of cases was registered), 40-64 years (+27.3%), over 65 years (+99.1%). These differences over the time in mortality changes are of great epidemiologic interest because of resulting possibilities for comparative investigation [20, 21, 22]. Mostly similar trends were found by Global Burden Disease study (GBD-2010), which estimated for the period 1990-2010 along with a slightly decreasing from major cardiovascular diseases premature mortality rates, there was also an increase of 17-28% for the potential years life lost from ischeamic heart diseases and cerebrovascular diseases [8, 9].

Conclusions

1. Despite the general decreasing trend of major cardiovascular diseases premature mortality rate, ischeamic heart diseases compared to cerebrovascular and hypertensive heart diseases identify the most pronounced trends of the deaths event rejuvenation in the Republic of Moldova for the period 2003-2015.

2. The systematic evaluation of premature mortality changes contributes to improve the quality assessment of the population health and evidence-based decision-making regarding the cardiovascular diseases prevention and control in the Republic of Moldova.

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Anatomic peculiarities of cervix uteri ligaments in pre- and postnatal human ontogenesis

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Abstract

Background: Uterus and uterine cervix ligament concept is a decisive factor for female pelvis surgery and for fundamental mechanisms of urogenital dysfunction ascertainment. According to publications, there are contradictory ideas of morphologic organization of female pelvis connective tissue. From this point of view necessity arises for system investigation of connective tissue around uterine and vagina in different age periods. Target: to ascertain peculiarities of uterine cervix ligaments macro- and micro-structure at 1st, 2nd adult, elderly and senile periods of ontogenesis.

Material and methods: Investigations have been performed in 35 anatomical specimens. The following investigational methods have been used: macroscopy, microscopy of consecutive histological sections series, conventional and thin preparations. Statistical data processing was performed with licensed program "Statistica" use. Received indices confidence was determined with Student's t-test use. Values with T<0,05 have been taken statistically significant.

Results: to ascertain peculiarities of uterine cervix ligaments their macro- and micro-structure in human ontogenesis using the morphologic and statistics methods.

Conclusions: The ligaments of uterine cervix have specific morphologic peculiarities of their structure and topography, and they contain different constituent parts in different age periods.

Key words: cervix uteri, human ontogenesis, ligaments, anatomy.

Introduction

"Uterus and uterine cervix ligament" concept is a decisive factor for female pelvis surgery and for fundamental mechanisms of urogenital dysfunction ascertainment [7, 9]. According to publications [10], there are two contradictory ideas of morphologic organization of female pelvis connective tissue. On the one hand, it is known, that pelvis connective tissue consists of anteroposterior and transversal systems. Anteroposterior system is formed by sagittal plate of dense connective tissue, expanding from pubic bones to sacral bone. Dorsal part of this system is called uterosacral or rectouterine ligament, and it has been described in detail by Campell [4]. Transversal system consists of the broad ligament, which caudal part is a so-called Mackenrodt's transverse ligament of the uterine cervix (UC) or Kocks's cardinal ligament. Other authors deny existence of ligaments, placed around uterine and vagina, at all [1]. From this point of view necessity arises for system investigation of connective tissue around uterine and vagina in different age periods.

Target: to ascertain peculiarities of uterine cervix ligaments macro- and micro-structure at 1st, 2nd adult, elderly and senile periods of ontogenesis.

Material and methods

Investigations have been performed in 35 anatomical specimens. The following investigational methods have been used: macroscopy, microscopy of consecutive histological sections series, conventional and thin preparations. Statistical data processing was performed with licensed program "Statistica" use. Received indices confidence was determined with Student's t-test use. Values with T<0,05 have been taken statistically significant. Investigation has been performed according to method recommendations of "Ethic and legislative regulations and requirements compliance at scientific morphologic investigation performance" and complying to basic provisions of the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects (1964-2000), and MoH of Ukraine Order of 23/09/2009 No 690.

Results and discussion

In embrionic period (9-10-weeks) pelvis cavity parts are filled with undifferentiated mesenchyme. Standard methods use does not permit to differentiate genital tube and adjoining tissue. The rectum of 9 week old embryos is covered with condensed mesenchyma layer, which is later differentiated to dense connective tissue. The urinary bladder, ventrally covered with condensed mesenchyma layer, has the appearance of the semicircle with a hole, located from backside. Lateral dilatations of the semicircle diverge from the urinary bladder wall in posterolateral direction. Nerves and vessels, entering the muscle layer of the urinary bladder, are located dorso-laterally, where the organ is covered by loose mesenchyme only. At 11th and 12th weeks of pre-fetus development mesenchyme in the pelvis region is replaced with loose connective tissue containing a large number of thin collagenic fibers. In 4-month fetuses the condensed mesenchyme layer is already presented by the dense connective tissue. At the urinary bladder cervix level it is directly linked with pubovesical ligament ventrally. Therefore, it is medially linked with parietal pelvic fascia. In 5-6-month fetuses takes place condensation of the pelvis connective tissue fibers. In 6-month fetuses the apex of the pelvis parietal fatty

layer penetrates to dense connective tissue layer plate of the urinary bladder ventrally and separates it to more thick medial and thinner lateral parts. In 5-7 fetuses differentiation of the connective tissue takes place, and it becomes possible to distinguish dense and loose connective tissue. Inside the pelvis cavity particles of fatty tissue are already formed, but differentiation and expansion of the fatty tissue is still in the process, therefore it is possible to detect clearly the organization of the pelvis connective tissue. Sacral bone does not have flexure yet, but coccyx flexure takes place in parallel to the rectum wall. Uterine body and UC in this development period are still placed in the same plane, anteflexio still exists. But due to the formed angle between vagina and UC one may say about anteversio. There is also insignificant flexture between cranial and caudal parts of vagina. Dense connective tissue is developed around uterine and vagina, and it is closely connected with subperitoneal connective tissue of rectouterine and vesicouterine recesses. At the level of these recesses there is a uterine body with wide ligaments on both sides located. Both peritoneal recesses are circularly covered with dense subperitoneal connective tissue. Thereby, ventral and dorsal subperitoneal layers of wide ligaments also consist of the dense connective tissue. Between these layers areolar connective tissue is detected, located along nerves and vessels of the uterine. Both, anterior and posterior uterine walls are covered tangentially with dense connective tissue. Subperitoneal connective tissue of the rectouterine recess consists of collagen fibers, whereas neither elastic fibers, nor smooth muscles cells have been detected. At the level of the caudal end of the rectouterine recess UC is dorsally embraced with dense connective tissue. Ventrally, loose connective tissue is located between the urinary bladder wall and UC wall. Connective tissue fibers are located tangentially along the UC posterior wall, and separate fibers are directed to its lateral wall. These fibers are also integrated into circular system and do not immediately fix the uterine to the pelvis lateral wall. Vagina posterior wall is loosely connected with rectal adventitia, its ventral wall conjugates tightly to urinary bladder and ureter walls with fibrous connective tissue. There were no definite uterine ligations detected. Adjoining to uterine and vagina connective tissue is an integral part of the neighboring structures. Rectouterine ligament (RUL) in 8-month fetuses is macroscopically visualized as a peritoneal fold only if fundus of uterus pulled off in anterior direction and fixed. Each fold connects UC with the sacral bone, being mildly fixed to the rectum medially. In histological sections RUL consisted of fatty and connective tissues, in which numerous vessels and nerve fibers have been detected. Moreover, clusters of sympathetic fibers were available in all cases, whereas there were no due ligament structures – histological signs of formed connective tissue were absent, small number of fibroblasts, fatty inclusions were available. In a newborn, fatty particles start expanding between dense connective tissue fibers of rectal adventitia. This layer is covered by the dense connective tissue plate, which may be considered a rectal fascia. It is clearly seen on pelvis parietal fascia at the level of the pelvic floor. Rectal vessels, nerves and lymph nodes are located inside rectal adventitia.

RUL is considered an important supporting structure together with vesicouterine, round ligaments, and paracervix [8]. Autonomous nerves of small pelvis organs, responsible for viscerosensory innervation of uterus, UC, vagina, ureter, urinary bladder, and rectum, are usually located within RUL. Thereby, in our judgment, such structure, as "ligament", is a complex, containing connective tissue, vessels, and nerves, integrated into visceral pelvic fascia (VPF).

At 1st, 2nd adult, elderly and senile ages RUL consists of two symmetric peritoneal folds along posterior uterine surface, forms curve around rectum and reaches pelvis surface of the sacral bone. RUL starts with fan-shaped fibers nearby sacral bone at the level S1-S3, sometimes at S4, proximally narrowing to UC. Two VPF folds, covering RUL behind uterine and laterally from the rectum, have been cut medially to ureters. There were lower inferior hypogastric plexus, hypogastric nerves and pelvis nerves detected between them. Hypogastric nerve fibers were located about 12,0-21,0 mm under each ureter. Hypogastric nerve is available in each side under ureter, goes posterior-anterior, top-down, and rounds RUL from the outer side. Pelvis nerves have been identified as derivatives of the third and the fourth anterior branches of sacral plexus, changing their direction down to RUL. They join, forming lower inferior hypogastric plexus in the lateral part of RUL and in the posterior layer of the broad ligament. Ureter is of great topographic significance, because it crosses lower inferior hypogastric plexus top-down, outside-inside. Distance from UC head to RUL – is 10.0-12.0 cm. RUL composition includes fatty inclusions, vessels, nerve fibers and clusters of sympathetic fibers. But there were larger amounts of fibroblasts and fatty tissue inclusions observed, compared to pre-natal ontogenesis period.

Anatomic investigation of RUL in any section reveals the availability of nerve fibers net in the connective tissue, which probably correspond to lower inferior hypogastric plexus, and it grounds the use of the term "ligamentous complex" [4, 6]. These ligaments are fixed to posterolateral UC wall at the level of the internal os. Near UC RUL have the appearance of clearly defined stripes, covered with peritoneum, but as they form in posterior direction upper border of the rectouterine pouch, they become rarer with less apparent folds of adjacent peritoneum [5]. Posterior one third of the ligament has fan-shaped form and consists of thinner fibers, fixed to presacral fascia, which is an integral part of the pelvis parietal fascia, located between fascial compartment of the rectum, upper fascia of pelvic diaphragm, and sacral bone, opposite from the lower part of the sacroiliac joint. RUL dimensions are 6.1±0.8 cm, 3.1±0.4 cm and 2.5±0.3cm in areas of sacral, intermediate, and cervix parts correspondingly. In the cervix end of ligaments there is a large number of vessels, which are branches of uterine arteries and veins. In perineal one third of the

RUL the moderate number of vessels is present, and in the sacral one – still lesser number. In posterior two thirds they consist of branch anastomoses of uterine and hemorrhoidal systems. It is often difficult to identify nerve components of these ligaments macroscopically. Parasympathetic nerve fibers of 2, 3, and 4 sacral segments may be detected in intermediate and anterior one thirds of RUL. They provide parasympathetic autonomous innervation of small pelvis organs. In the location of the RUL cervix fixing, there are sympathetic fibers detected, reaching UC, which accompany uterine artery, and just they provide uterine sympathetic vegetative innervation. In the process of VPF ectomy, nerve fibers have been detected, leading from UC to the sacral bone. Anatomic and histologic peculiarities in further periods do not differ considerably; there are nerve fibers, sympathetic fibers clusters, and arterial, venous and lymph vessels inside connective tissue available too. Histologically RUL may be divided into 3 parts. Anterior or cervix department contains smooth muscles, which amount is dominating among all listed components, fibroelastic connective tissue, blood and lymph vessels, and nerves. In intermediate RUL one third dominating tissue component is connective tissue. There is a dense connective tissue layer available, located lower than peritoneum, which may be considered "a fibrous layer". Intermediate one third consists of the connective tissue, concentrated in subserous fibrous layer, under which there is a less dense net of chaotically expanded fibers of connective tissue. Nerves elements are numerous, and blood vessels are available in moderate number. In this region smooth muscle fibers and lymph vessels are detected here and there. Posterior or sacral part is almost completely composed of loose connective tissue and fatty inclusions. Insignificant number of blood and lymph vessels is present here.

It was established that transverse cervical ligament (TCL) in the 1st, 2nd adult, elderly and senile ages is a mesenteric-like structure, anteriorly and posteriorly covered with VPF, and it is an extention of the perivascular cover of internal and external iliac arteries and veins [3]. Pelvis organs in their natural position, and without pathologies, do not have expressed structures of ligament nature in the area of TCL. TCL total length is 8.0-10.0 cm on average, it may be conditionally divided into such departments: distal (cervix) department 2.0±0.2 cm thick and 2.1±0.3 cm long; intermediate department 3,4±0,2 cm long and 1,8±0,2 cm wide; proximal (pelvis) department has triangular form in transverse incision, its length is 4,6±0,3 cm and the largest width is 2,1±0,2 cm. In the distal department TCL is fixed to the UC lateral surface. In the rear side it is connected with RUL fixing place. TCL is caudally connected with the upper fascia of the pelvis diaphragm (nearby levator ani). In the intermediate department there were observed noticeable ventral (vessel) and dorsal (nerve) areas, ureter was visualized, which along surface was crossed by uterine artery and vein; located in depth branches of uterine veins often separated ureter from nerve structures of the dorsal part. In the proximal department fixing place of TCL to the lateral pelvis wall had triangular form, which top is the 1st diverticulum of the internal iliac artery, and basis is an upper fascia of the pelvis diaphragm. Loose connective tissue, surrounding blood vessels and pelvis nerve plexus, appears nearby hypogastric artery and occupies large anterior and medial area, reaches lateral UC surface; it contains less fat and is more compact, than the rest of the retroperitoneal loose connective tissue. This condensing is mostly expressed at lateral surfaces of UC and vagina, and expands down to the level of the pelvic floor. It cannot be separated from thinner parietal pelvis fascia, but this structure does not expand around vagina and UC. Laterally to the uterine artery vessels number grows, loose connective tissue becomes less compact and it is loosely connected with upper fascia of pelvis diaphragm by several thin fibers. While approaching the pelvis wall these tissues fan-shapely expand and continuously connect to the retroperitoneal connective tissue. With uterine pulled off to the opposite side, more differentiated tissue structure becomes evident, which may be easily distinguished from the areolar tissue, located in front of it, and from pelvis parietal fascia, located behind, around the rectum. Vessels are located in the area between two thick stripes, which pass from the lateral edges of UC and vagina to the pelvis lateral wall nearby the top of the hypogastric artery. The most part of TCL contains blood vessels (mostly veins), nerves, originating in the pelvis plexus, lymph vessels, and adjacent loose connective tissue. Paracervix may be identified as cardinal ligament due to its strength, and it surrounds so-called venous "root", it is formed from one or more transversally oriented venous vessels, overlying one another and joining to paravisceral venous plexus into the subperitoneal vein [2]. Microscopic investigation established, that TCL main mass includes blood vessels (mostly veins), nerves of the lower inferior hypogastric plexus, lymph vessels, and areolar connective tissue, surrounding these structures. There are joints of collagen thin fibers with upper fascia of the pelvis diaphragm available. Loose connective tissue is the densest in the area, where blood vessels penetrate the fascia. Plain muscle fibers are present in blood vessels walls and adventitia composition only. There was large amount of cell elements, especially fibroblasts observed. Several isolated elastic fibers outside vessel walls have been detected. Thereby, TCL consists mostly of vessels, loose connective tissue and separate nerve fibers. It may be divided into vessel ((cranial, parametrium)) and nerve (tail, paracervix) parts. Vessel area is a prolongation of the perivascular cover of internal iliac vessels, leading to genital roots, whereas nerve part is a prolongation of the inferior hypogastric plexus.

Pubocervical ligament (anterior ligament) consists of vesicouterine fold of peritoneum, which is projected onto the urinary bladder from the anterior part of uterine, at the border of UC and body, and changes during human ontogenesis are almost absent.

Conclusions

1. In 9-10-week embryos pelvis cavity departments are filled with undifferentiated mesenchyme. In 11-12-week pre-fetuses mesenchyme in the pelvis area is replaced by areolar connective tissue, containing large number of thin collagen fibers. In 4-month fetuses the condensed mesenchyme layer is already presented by the dense connective tissue.

2. In 5-7 month fetuses differentiation of connective tissue occurs, areolar and dense connective tissues are distinguished. Dense connective tissue develops around uterine and vagina and is tightly tied with subperitoneal connective tissue of rectouterine and vesicouterine pouches.

3. At 1st, 2nd adult, elderly and senile ages the uterine cervix transverse ligament is a mesenteric-like structure 8,0-10,0 cm long, anteriorly and posteriorly covered with visceral pelvis fascia, and contains vessels, loose connective tissue and separate nerve fibers, and has cervix, intermediate and distal departments.

4. In the cervix end of the rectouterine ligament there is a large number of vessels available, which are branches of uterine arteries and veins, it contains smooth muscles, dense connective tissue, blood and lymph vessels, and nerves; in the intermediate one third vessels are present in moderate number, main tissue component is connective tissue; and in the sacral one – even less, it consists of loose connective tissue and fatty inclusions.

5. Rectouterine ligament dimensions are 6.1±0.8cm, 3.1±0.4cm i 2.5±0.3cm in areas of sacral, intermediate and cervix departments correspondingly.

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Management of Delphi study regarding the development of ongoing behavioral risk factor surveillance system in the Republic of Moldova

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Abstract

Background: Implementation of ongoing behavioral risk factor surveillance system (BRFSS) can improve prevention and control of noncommunicable diseases (NCDs) in the Republic of Moldova. Delphi study regarding the development of ongoing behavioral risk factor surveillance system in the Republic of Moldova contributes to evidence-based credible model of implementation in order to support National Strategy on Noncommunicable Diseases Prevention and Control for the period 2012-2020. The article has highlighted the aspects of designing Delphi survey which should be considered for making sense of consensus.
Material and methods: The study used Delphi techniques to achieve in an effective way experts' consensus in terms of development of ongoing BRFSS in the Republic of Moldova.
Results: The research found that Delphi panelists similarly trained and competent in the area of knowledge related to the target issue contributed to achievement of the consensus agreement for all items in discussion regardless the national or international affiliation.
Conclusions: Well-designed Delphi panel are important for effective and reasonable survey management in terms of achieving feasible consensus agreement to support effective decision-making for further development.

Key words: Delphi study, ongoing behavioral risk factor surveillance system.

Introduction

Ongoing surveillance of behavioral risk factors is a powerful tool in reducing mortality from noncommunicable diseases [1, 2]. Proportional mortality from noncommunicable diseases is 89% in the Republic of Moldova [3]. There is no system for ongoing surveillance determining the interventions priorities regarding behavioral risk factors in the Republic of Moldova.

The objective of the study was to determine experts' consensus on a variety of national and international health policies in terms of development ongoing Behavioral Risk Factors Surveillance System in the Republic of Moldova.

Delphi method is a procedure that allows a group of experts to participate jointly but anonymously by many rounds of questionnaires, in order to reach consensus for forecasting, planning or for strategies development questions [4]. The Delphi survey has been performed in order to provide good practice evidences for potential implementation of behavioral surveillance system in the Republic of Moldova, adjusted to the local needs supporting the National Strategy on Noncommunicable Diseases Prevention and Control for the period 2012-2020 [5].

Material and methods

The Delphi survey was performed for a period of 8 months, from July 2016 till February 2017. The Delphi study included two written Delphi rounds to complete a questionnaire via e-mail. The selection was based on including national and international professionals in the field of management of risk factors surveillance, using snowball-sampling design. Invited international experts were from countries with ongoing surveillance system based on BRFSS U.S standards. Delphi panel included 19 public health experts from USA, Italy, Romania and the Republic of Moldova, who accepted the invitational letter sent individually to the list of 55 potential participants.

The first questionnaire was prepared based on the issue areas of behavioral risk factors control and prevention at the national and international level [5, 6, 7]. The questions content was a result of many different sources, as following: Action Plan for the period 2016-2020 regarding the implementation of National Strategy on noncommunicable diseases prevention and control 2012-2020 [8], Action Plan for the period 2014-2020 regarding the implementation of National Program on cardiovascular diseases prevention and control for the period 2014-2020 [9], research findings from pilot cross-sectional telephone survey test conducted in the Municipality of Chisinau of the Republic of Moldova (n=800) mainly based on the US BRFSS's protocol [10], and review of recent publications on national ongoing behavioral risk factor surveillance systems [11, 12, 13]. A 9-point Likert agreement scale was used to measure the strength of the experts' consensus with a clear statement (from 1 being completely disagreed to 9 being completely agreed). The core part of the first round questionnaire (38 items) was structured around the US BRFSS's protocols [1] and tasks regarding the evaluation of a public health surveillance system mainly based on Updated Guidelines for Evaluating Public Health Surveillance Systems [14], as follows: purpose (9 items), operation (15 items), and attributes (14 items) of the surveillance system.

Pilot round questionnaire was performed with participation of three experts not belonging to the written Delphi panel.

The questionnaire for the second round was based on the results and comments of the first round.

The statistical analyses were performed using Excel for Mac 2011(version 14.7.2) and PSPP (version 0.8.4) which is free software application for analyses data, intended as free alternative for IBM SPSS Statistics. The five number sum-

maries were used to present the information regarding the consensus of the Delphi panel experts. Boxplots graph presentation was used to display five number summaries: the ends of whiskers are the minimum and maximum values, the bottom and top of the box indicate Q_1 and Q_3 respectively, and the median is displayed by the band inside box. A Fisher's Exact test was applied to assess the significance between two independent groups. The significance level was set at a 2-sided of .05

A criterion for achieved consensus of the experts on a nine point Likert rating score is considered if the median has to be at seven or higher.

Results

All experts who accepted the invitation to join the Delphi study panel completed the first round questionnaire consequently no dropout rate was registered. The first round Delphi survey included 19 participants with 9 international and 10 national experts.

The strength of the experts' consensus for all items included in the first questionnaire compartment of the purpose (9 questions) of Behavioral Risk Factor Surveillance System development in the Republic of Moldova was at the median score from 8.5 to nine points. The items related to the operation (15 questions) of the surveillance system were at the median score from seven to nine (fig. 1).

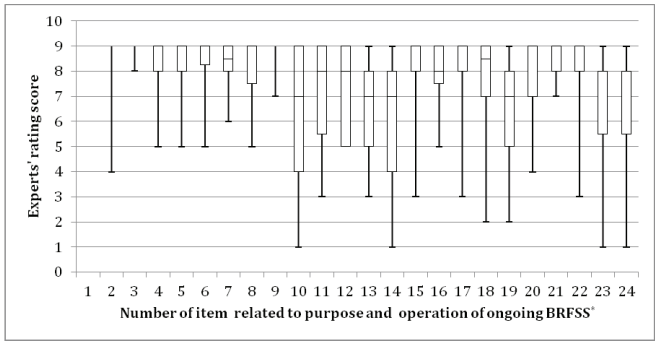

Fig. 1. Distribution of experts' score by nine point Likert scale regarding the items related to purpose and operation of ongoing behavioral risk factor surveillance system development in the Republic of Moldova.

*Abbreviations: BRFSS, Behavioral Risk Factor Surveillance System

The contents of core questions related to purpose and operation of ongoing behavioral risk factor surveillance according to their number were, as following:

Purpose of ongoing BRFSS

Health-related risk factor events under surveillance:

In terms of providing a complex surveillance of risk factors, the system is required to take into account the following events:

1. Behavioral risk factors: smoking status, healthy diet, alcohol consumption, and physical activity.
2. Biological risk factors: blood pressure, total serum cholesterol, fasting blood glucose, and body mass index.
3. Ongoing surveillance of modifiable risk factors is required along with monitoring of individual coexisting morbidities.

Surveillance indicators:

Calculation of core monitoring indicators in terms of:

4. Events related to monitoring indicators.
5. Quality related indicators of system performance (Response rates).
6. Indicators must respect international common standards.

Level of integration:

In terms of providing an integrated surveillance of risk factors, the system is required to take into account the following:

7. Using the standards of existing ongoing BRFSS, which permits comparability among surveys at the international level.
8. Ongoing surveillance of modifiable risk factors is required along with monitoring of mortality (inclusively premature deaths) and morbidity, all being integrated as an informational system.
9. A systematic and ongoing approach in the surveillance of risk factors helps to provide useful information for the continual monitoring of public health trends.

Operation of ongoing BRFSS

Population under surveillance:

In terms of premature deaths, assessment is more logical and efficient:

10. The study population should consist of persons aged between 18 and 69 years old *rather than* the study population consisting of persons aged 18+ years old.

In terms of mitigating falling survey resolution and response rate, it is more logical and efficient to:

11. Use an approach to select respondents enrolled in the lists of local health units vital statistics, updated on 1st January of the year of the survey *than* to use the Random Digit Dialing (RDD) approach to select the phone numbers by randomly selecting from commercially available lists of telephone numbers.

Period of data collection:

In order to mitigate falling survey response rates, it is more logical and efficient to do:

12. Sampling based on a monthly collection switched to a four month reporting frame which *may* provide more time to contact respondents for a refusal conversation

Data collection:

In order to mitigate falling survey response rates, it is more logical and efficient:

13. To provide telephone interview data collection by a Local Health Unit (LHU) working team comprised of coordinators (family doctor, statistician), interviewers (nurses), and public health professionals.
14. To provide telephone interview data collection by a Local Public Health Unit (LPHU) working team comprised of several public health professionals and statisticians.
15. For each unit the monthly, and respectively, annual minimum sample size of completed interview is defined at the beginning of year.

Data management:

16. National coordinating group supervises the application of methods and standards of the process.

17. National technical group supervises process of verification and correction of the interviews and makes available dataset after prior quality controls are applied to programs.
18. Regional coordinating group gives assistance and support to the local working teams.

Funding sources:

19. New implementation of BRFSS using existing Health System organization and management provide affordable expenditures.

Personnel requirements:

20. Trained staff at the local level conducts telephone survey.
21. Technical and methodological assistance for training is provided by a coordinating group at the National level.
22. Local working group is composed of coordinators, interviewers, and public health experts.
23. Coordinators are a medical doctor and a statistician already working in local health unit.
24. Interviewers are nurses already working in local health unit.

Consensus of the Delphi survey experts in terms of attributes (14 questions) of the ongoing surveillance system found potential implementation in the Republic of Moldova as falling within 7-9 median score (fig. 2).

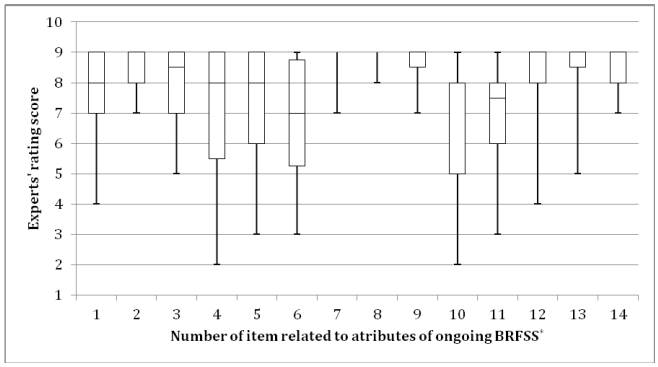

Fig. 2. Distribution of experts' score by nine point Likert-scale regarding the items related to attributes of ongoing behavioral risk factor surveillance system development in the Republic of Moldova.

*Abbreviations: BRFSS, Behavioral Risk Factor Surveillance System.

The contents of core questions related to attributes of ongoing behavioral risk factor surveillance according their number were as following:

Simplicity:

1. Flow chart is structured according to three distinct levels: national, regional and local.
2. To determine standards for system operation and assessing the performance.

Flexibility:

3. Along with a fixed core component of the questionnaire, it is required to provide rotating core components *(sets of questions, asked in alternating years by all participating Local Health Units that address different topics).*
4. Along with fixed core components of the questionnaire, it is required to provide optional modules *(questions that regions select in their questionnaires to achieve needed information).*
5. Along with fixed core component of the questionnaire, it is required to provide emerging modules *(a few questions for brief periods of time).*
6. Only fixed core components of questionnaire are required to be provided during the implementation period (*sets of standardized questions, asked in different periods of time by all participating local health units).*

Data quality:

7. To utilize the Nationwide standardized structured questionnaire and the surveillance indicators calculation.
8. To share a common information system and database.
9. To provide central supervision and support for training, data analyses and communications activities.

Acceptability:

10. Extracting the sample from local health units' lists of residents vs. extracting the sample from random digit dialing will improve respondent's accessibility.
11. Data collection provided by local health units versus data collection provided by public health units will improve respondent's cooperation.

Sensitivity:

12. Health literacy level improves the ability of persons to understand the questions and correctly identify their status.
13. Continued information about the surveillance system provided not only on regular medical check–up visits but also through the media will improve the willingness of respondents to report their status.

Timelines:

14. Electronic data collection from reporting sources including entry data by web-based system (local/regional/national access).

When comparing the opinion of international and national experts for every 38 items from core part of the first round questionnaire in 94.7% of cases the significant difference was not observed ($p > .05$). The opinion of international and national experts was significantly different in case of two questions: one related to surveillance system purpose (item number 6; p=.033) and other related to surveillance system operation (item number 10; p=.019).

The dropout rate for the second round was 21.1% with 15 experts participating (7 international and 8 national). Due to the first round Delphi survey achieved experts' consensus in all items included for discussions, the second round questionnaire was composed of a few questions only to gather experts' suggestions and recommendations in order to provide some specific additional details for reached consensus before.

Discussion

In the literature the optimal number of subjects to involve in the Delphi study is not really defined [15]. However, when the training of experts is similar, ten to fifteen Delphi

panel participants are sufficient for useful results, even found between five and ten members are reasonable [16,17].

Following the recommendation of previous Delphi study about the importance of high homogeneity of the experts' panel regarding the similar training and general understanding in the field of interest, this study reached the opinions' consensus in the first round of the Delphi written survey with the relatively reasonable numbers (19) of participants. This unexpected rapid consensus achievement could be explained by homogeneity of Delphi panel considered as study strengths as well, along with anonymity and joint but individual thinking. Although however it should be noted that Delphi participants from countries developing ongoing BRFSS based on U.S. standards were underrepresented, as their participation agreement has not been obtained.

This study found that national and international experts highly trained and competent in the area of knowledge related to the target issue mainly expressed (94.7%) the similar opinion. This finding is particularly important to highlight that expectations and needs of ongoing system potential implementation in the Republic Moldova are similarly directed to the recommendations and suggestions of functional and successful ongoing surveillance system in the world, being a great opportunity for feasible development of ongoing BRFSS in the Republic of Moldova.

Limitations of this study are: confusion around the Delphi sample size, non-probability method of sampling, self-reporting data and mainly qualitative approach of the research.

Conclusions

High homogeneity of Delphi panel related to similar trained and competent experts allows for effective and reasonable survey management in terms of achieving feasible consensus agreement.

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